



POLYPEPTIDE HAVING AN ACTIVITY TO SUPPORT PROLIFERATION
OR SURVIVAL OF HEMATOPOIETIC STEM CELL AND HEMATOPOIETIC
PROGENITOR CELL, AND DNA CODING FOR THE SAME

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Background of the Invention

Field of the Invention

The present invention relates to a polypeptide having an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells, a DNA coding the polypeptide, and a pharmaceutical composition comprising the polypeptide as active ingredient.

Description of the Related Art

15 Fully differentiated mature hematopoietic cells have limited short lives. Homeostasis of the blood is maintained due to supply of the mature blood cells caused by continuous differentiation of hematopoietic progenitor cells. The hematopoietic progenitor cells
20 are giving rise from more undifferentiated hematopoietic stem cells. The hematopoietic stem cells have potential of differentiating into all of the differentiation lineages (totipotency) and have potential of self-renew with retaining the totipotency
25 so as to supply the hematopoietic cells through life. That is, the hematopoietic stem cells are known to generate totipotent stem cells by the self-renew and to

differentiate in parts to a variety of the mature blood cells through the hematopoietic progenitor cells.

This differentiation of the blood cells is regulated by a variety of cytokines. Erythropoietin is known to 5 promote the differentiation of the erythrocytic lineages. G-CSF and thrombopoietin are also known to promote the differentiation of the neutrophils, and the megakaryocytes and the platelet productive cells, respectively. However, a factor required for the self- 10 renew of the hematopoietic stem cell with retaining the totipotency has not been clear. Although SCF/MGF (Williams, D.E., *Cell*, 63: 167-174, 1990; Zsebo, K.M., *Cell*, 63: 213-224, 1990), SCGF (WO98/08869), and the like are reported as growth factors for the 15 hematopoietic stem cells, none of them have potency to sufficiently retain the totipotency of the hematopoietic stem cells. Although attempts to culture the hematopoietic stem cells in the presence of combinations of known cytokines, a system for efficient amplification 20 of the hematopoietic stem cells was not realized (Miller, C. L., *Proc. Natl. Acad. Sci. USA*, 94: 13648-13653, 1997; Yagi, M., *Proc. Natl. Acad. Sci. USA*, 96: 8126-8131, 1999; Shih, C.C., *Blood*, 94: 5 1623-1636, 1999).

On the other hand, attempts to allow the 25 hematopoietic stem cells to survive or proliferate without differentiation by using stromal cells which supply an environment suitable for survival or

proliferation of the hematopoietic stem cells were reported (Moore K.A., *Blood*, 89: 12, 4337-4347, 1997). In addition, WO99/03980 discloses a stromal cell line capable of supporting proliferation or survival of 5 hematopoietic stem cells and hematopoietic progenitor cells, which are established from an AGM (Aorta-Gonad-Mesonephros) region of a fetal mouse.

It is postulated that there should be more peptides that efficiently facilitate hematopoietic stem cell and 10 progenitor cell amplification by themselves or in combination with stromal cells or stimulating factors such as cytokines, in addition to known factors affecting hematopoietic cells.

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Summary of the Invention

Since the proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells *in vitro* can be supported by co-culture of stromal cells and hematopoietic stem cells and hematopoietic progenitor 20 cells, the stromal cells are expected to produce factors supporting the proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells. An object of the present invention is to provide a factor supporting the proliferation or survival of 25 hematopoietic stem cells or hematopoietic progenitor cells, which is derived from the stromal cells.

The inventor of the present invention has assumed

that the mouse stromal cells produce factors supporting the proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells, as mentioned above. Attention is given that there are two kinds of 5 stromal cells. One has a ability to support the proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells (hereafter sometimes referred to as "activity to support hematopoietic stem cells"). The other does not have the activity to 10 support hematopoietic stem cells. The inventor of the present invention has assumed that this difference in the ability is due to the fact that expression of genes encoding the factors is increased in the supporting stromal cells and that the expression is low in non- 15 supporting stromal cells. Thus the inventor think it can be found the factors supporting the proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells among the genes expressed higher in the supporting cells compared to in the non-supporting cells. 20 In this context, the inventor has identified genes of which expressions are high in AGM-s3-A9 cell line which has the activity to support hematopoietic stem cells, and low or undetected in AGM-s3-A7 cell line which does not have the activity to support hematopoietic stem 25 cells, and has determined the activities to support hematopoietic stem cells, of cells in which these gene groups are highly expressed. As a result, the present

invention has been completed.

That is, the present invention provides the followings.

(1) A DNA coding for a polypeptide of the
5 following (A) or (B):

(A) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 23 and SEQ ID NO: 25; or

(B) a polypeptide which comprises an amino acid 10 sequence including deletion, substitution or insertion of one or several amino acids in the amino acid sequence as defined in (A), and which has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

15 (2) The DNA according to (1), which is a DNA of the following (a) or (b):

(a) a DNA which comprises a nucleotide sequence selected from the group consisting of the nucleotide sequence of nucleotides 1 to 444 of SEQ ID NO: 18, the 20 nucleotide sequence of nucleotides 630 to 1358 of SEQ ID NO: 22, nucleotides 132 to 506 of SEQ ID NO: 24, and the nucleotide sequence of nucleotides 18 to 746 of SEQ ID NO: 47; or

(b) a DNA which is hybridizable with a DNA comprising 25 the nucleotide sequence as defined in (a) or a probe prepared from said DNA, under the stringent condition, and which has an activity to support proliferation or

survival of hematopoietic stem cells or hematopoietic progenitor cells.

(3) The DNA according to (2), the stringent condition is 6 x SSC, 5 x Denhardt, 0.5% SDS and 68°C
5 (SSC: 3 M NaCl, 0.3 M sodium citrate; 50 x Denhardt: 1% BSA, 1% polyvinyl pyrrolidone, 1% Ficoll 400), or 6 x SSC, 5 x Denhardt, 0.5% SDS, 50% formamide and 42°C.

(4) A expression vector which comprises the DNA of any one of (1) to (3) in such a manner that the DNA
10 can be expressed.

(5) A cell into which the DNA of any one of (1) to (3) is introduced in such a manner that the DNA can be expressed.

(6) A polypeptide which is an expression product
15 of the DNA of any one of (1) to (3), the polypeptide having an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

(7) The polypeptide according to (6), which
20 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 23, SEQ ID NO: 25 and SEQ ID NO: 48, or an amino acid sequence including deletion, substitution or insertion of one or several amino acids in the amino acid sequence.

25 (8) The polypeptide according to (6) or (7), which is modified with one or more modifying agents selected from the group consisting of polyethylene

glycol (PEG), dextran, poly(N-vinyl-pyrrolidone), polypropylene glycol homopolymer, copolymer of polypropylene oxide/ethylene oxide, polyoxyethylated polyol and polyvinyl alcohol.

5 (9) An monoclonal antibody which binds to the polypeptide of any one of (6) to (8).

(10) A method for supporting proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells, comprising the step of co-culturing 10 stromal cells in which a DNA coding for a polypeptide of the following (A) or (B) is expressed, with hematopoietic stem cells or progenitor cells,

(A) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID 15 NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, and SEQ ID NO: 48; or

(B) a polypeptide which comprises an amino acid 20 sequence including deletion, substitution or insertion of one or several amino acids in the amino acid sequence as defined in (A), and which has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

25 (11) The method according to (10), wherein the DNA is a DNA of the following (a) or (b):

(a) a DNA which comprises a nucleotide sequence

selected from the group consisting of the nucleotide sequence of nucleotides 1 to 1671 of SEQ ID NO: 8, the nucleotide sequence of nucleotides 1 to 1674 of SEQ ID NO: 10, the nucleotide sequence of nucleotides 1 to 366 of SEQ ID NO: 12, the nucleotide sequence of nucleotides 84 to 1121 of SEQ ID NO: 14, the nucleotide sequence of nucleotides 1 to 1035 of SEQ ID NO: 16, the nucleotide sequence of nucleotides 1 to 444 of SEQ ID NO: 18, the nucleotide sequence of nucleotides 1 to 444 of SEQ ID NO: 20, the nucleotide sequence of nucleotides 630 to 1358 of SEQ ID NO: 22, the nucleotide sequence of nucleotides 132 to 506 of SEQ ID NO: 24, the nucleotide sequence of nucleotides 1 to 2487 of SEQ ID NO: 26, and the nucleotide sequence of nucleotides 1 to 2496 of SEQ ID NO: 28, and nucleotides 18 to 746 of SEQ ID NO: 47; or

(b) a DNA which is hybridizable with a DNA comprising the nucleotide sequence as defined in (a) or a probe prepared from said DNA, under the stringent condition, and which has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

(12) A method for supporting proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells, comprising the step of culturing hematopoietic stem cells or progenitor cells in the presence of a polypeptide of the following (A) or (B),

said polypeptide having an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells when the hematopoietic stem cells or hematopoietic progenitor cells are 5 cultured in the presence of the polypeptide,

(A) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, 10 SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, and SEQ ID NO: 48; or

(B) a polypeptide which comprises an amino acid sequence including deletion, substitution or insertion of one or several amino acids in the amino acid sequence 15 as defined in (A), and which has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

(13) A pharmaceutical composition having an effect to support proliferation or survival of 20 hematopoietic stem cells or hematopoietic progenitor cells, which comprises an effective amount of a polypeptide of the following (A) or (B), said polypeptide having an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic 25 progenitor cells when hematopoietic stem cells or hematopoietic progenitor cells are cultured in the presence of the polypeptide,

(A) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, 5 SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, and SEQ ID NO: 48; or

(B) a polypeptide which comprises an amino acid sequence including deletion, substitution or insertion of one or several amino acids in the amino acid sequence 10 as defined in (A), and which has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

Terms used in this specification are defined as follows.

15 A hematopoietic stem cell is defined as a cell having totipotency, that is, ability to differentiate into all the cell lineages of the blood cells, and having a potency of self-renew with retaining the totipotency. A hematopoietic progenitor cell is defined 20 as a cell which can differentiate a single cell lineage of the blood cell or plural cell lineages but cannot differentiate into all of the cell lineages. A stromal cell is defined as a cell which can be co-cultured together with the hematopoietic stem cells to construct 25 a hematopoietic environment simulating *in vivo* hematopoietic environment *in vitro*. Cells derived from any origin can be used as long as the cells can be co-

cultured with the hematopoietic cells *in vitro*.

Erythrocyte progenitor cells hardly survive and proliferate in *in vitro* culture environments and rapidly disappear. If the survival and proliferation of the erythrocyte progenitor cells are observed, continuous production of the erythrocyte progenitor cells is predicted to occur due to the survival and proliferation of the more immature hematopoietic stem cells or the hematopoietic progenitor cells. Therefore, in an assessment system of human hematopoietic stem cells, proliferation of hematopoietic stem cells or immature hematopoietic progenitor cells can be determined by using the survival and proliferation of the erythrocyte progenitor cells (BFU-E, CFU-E, and CFU-E mix) as an index.

Brief Explanation of the Drawings

Fig. 1 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-s3 subclone A9, A7, or D11 cells for two weeks.

Fig. 2 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-s3 subclone A9, A7, or OP9 cells for two weeks.

Fig. 3 shows time course of donor derived lymphoid lineage cells or myeloid lineage cells reconstitution in irradiated recipient mice that received the hematopoietic stem cells co-cultured with stromal cells.

5 Fig. 4 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-S3-A9 cells in which a gene SCR-2 is highly expressed (A9/SCR-2), AGM-S3-A9
10 cells into which a control vector is introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks.

Fig. 5 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive
15 hematopoietic stem cells with AGM-S3-A7 cells in which a gene SCR-2 is highly expressed (A7/SCR-2), AGM-S3-A7 cells into which a control vector is introduced (A7/pMXIG) or AGM-S3-A7 cells (A7) for two weeks.

Fig. 6 shows time course of donor derived lymphoid
20 lineage cells or myeloid lineage cells reconstitution in peripheral blood of irradiated recipient mice that received the hematopoietic stem cells co-cultured with AGM-S3-A7 cells in which a gene SCR-3 is highly expressed (A7/SCR-3), AGM-S3-A7 cells into which a
25 control vector is introduced (A7/pMXIG) or AGM-S3-A7 cells.

Fig. 7 shows proliferation statuses of hematopoietic

stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-S3-A9 cells in which a gene SCR-4 is highly expressed (A9/SCR-4), AGM-S3-A9 5 cells into which a control vector is introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks.

Fig. 8 shows time course of donor derived lymphoid lineage cells or myeloid lineage cells reconstitution in peripheral blood of irradiated recipient mice that 10 received the hematopoietic stem cells co-cultured with AGM-S3-A7 cells in which a gene SCR-5 is highly expressed (A7/SCR-5), AGM-S3-A7 cells into which a control vector is introduced (A7/pMXIG) or AGM-S3-A7 cells.

15 Fig. 9 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-S3-A9 cells in which a gene SCR-6 is highly expressed (A9/SCR-6), AGM-S3-A9 20 cells into which a control vector is introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks.

Fig. 10 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells determined by a clonogenic assay after co-culture 25 of CD34-positive hematopoietic stem cells with AGM-S3-A9 cells in which a gene SCR-7 is highly expressed (A9/SCR-7), AGM-S3-A9 cells into which a control vector is

introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks.

Fig. 11 shows proliferation statuses of hematopoietic stem cells and hematopoietic progenitor 5 cells determined by a clonogenic assay after co-culture of CD34-positive hematopoietic stem cells with AGM-S3-A9 cells in which a gene SCR-8 is highly expressed (A9/SCR-8), AGM-S3-A9 cells into which a control vector is introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two 10 weeks.

Detailed Description of the Invention

Hereafter, the present invention will be described in detail below.

15 The following genes are those identified as genes of which expressions are high in AGM-s3-A9 cell line which has the activity to support hematopoietic stem cells, and low or undetected in AGM-s3-A7 cell line which does not have the activity to support hematopoietic stem 20 cells, and determined to have the activities to support hematopoietic stem cells, of cells in which these gene groups are highly expressed.

Gene SCR-2

25 The gene is the same gene as a mouse gene, *Mus musculus glypican-1 (GPC-1)* of a GenBank accession number AF185613.

The nucleotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 8. Only the amino acid sequence is shown in SEQ ID NO: 9.

5 The human amino acid sequence of GPC-1 is recorded in GenBank under an accession number P35052, and the human nucleotide sequence of GPC-1 is recorded in GenBank database under an accession number AX020122. It is predicted that the similar activity is detected in
10 the human gene.

The nucleotide sequence of the gene from human and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 10. Only the amino acid sequence is shown in SEQ ID NO: 11.

15 Glypican is a major hepran sulfate proteoglycan existing on a cell surface, and have a characteristic structure such as cysteine rich globular domain, short glycosaminoglycan binding domain, glycosylphosphatidyl-inositol membrane binding domain. Six family genes from
20 glypican-1 to glypican-6 have been found (J Biol Chem 1999 Sep 17;274(38):26968-77. Glypican-6, a new member of the glypican family of cell surface heparan sulfate proteoglycans. Veugelers M, De Cat B, Ceulemans H, Bruystens AM, Coomans C, Durr J, Vermeesch J, Marynen P,
25 David G).

With respect to biological activities of GPC-1, there are a number of reports: To regulate growth

stimulating activity of heparin binding growth factors (fibroblast growth factor 2 (FGF2), heparin-binding EGF-like growth factor (HB-EGF)) to promote proliferation of cancer cells showing autocrine proliferation by

5 stimulation by the growth factors (J Clin Invest 1998 Nov 1; 102(9):1662-73, The cell-surface heparan sulfate proteoglycan glypican-1 regulates growth factor action in pancreatic carcinoma cells and is overexpressed in human pancreatic cancer., Kleeff J, Ishiwata T, Kumbasar 10 A, Friess H, Buchler MW, Lander AD, Korc M).

To bind HGF (hepatocyte growth factor) to promote reactivity with cytokines, of antigen-specific B cells.

To participate in association of a cell with an adhesive molecule to involve in invasion of the cell (J Biol Chem 15 1998 Aug 28;273(35):22825-32, Heparan sulfate proteoglycans as adhesive and anti-invasive molecules. Syndecans and glypican have distinct functions., Liu W, Litwack ED, Stanley MJ, Langford JK, Lander AD, Sanderson RD). These findings show that GPC-1 involves 20 in activity expression of various cell-stimulating factors. Also, there is a report that expression of the glypican family gene in bone marrow is confirmed (Biochem J 1999 Nov 1;343 Pt 3:663-8, Expression of proteoglycan core proteins in human bone marrow stroma., 25 Schofield KP, Gallagher JT, David G). However, in these reports, it is not described about effects of GPC-1 on hematopoietic stem cells or hematopoietic progenitor

cells.

Gene SCR-3

The gene is the same gene as mouse genes, *Mus musculus* chemokine MMRP2 mRNA of a GenBank accession number U15209, *Mus musculus* C10-like chemokine mRNA of U19482 and mouse macrophage inflammatory protein-1gamma mRNA of U49513.

The nucleotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 12. Only the amino acid sequence is shown in SEQ ID NO: 13.

Gene SCR-4

The nucleotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 14. Only the amino acid sequence is shown in SEQ ID NO: 15.

It has been found that the sequence has a high homology to *Homo sapiens* clone 25077 mRNA of a GenBank accession number AF131820, and that it is considered to be a mouse ortholog. This sequence is described in WO 00/66784.

The nucleotide sequence of the gene from human and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 16. Only the amino acid sequence is shown in SEQ ID NO: 17.

Gene SCR-5

The nuclotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide 5 sequence are shown in SEQ ID NO: 18. Only the amino acid sequence is shown in SEQ ID NO: 19.

It has been found that the sequence has a high homology with *Homo sapiens* esophageal cancer related gene 4 portein (ECRG4) mRNA of a GenBank accession 10 number AF325503, and that it is considered to be a mouse ortholog of AF325503.

The nuclotide sequence of the gene from human and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 20. Only the amino 15 acid sequence is shown in SEQ ID NO: 21.

Gene SCR-6

The nuclotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide 20 sequence are shown in SEQ ID NO: 22. Only the amino acid sequence is shown in SEQ ID NO: 23.

The nuclotide sequence of the gene from human and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 47. Only the amino 25 acid sequence is shown in SEQ ID NO: 48.

Gene SCR-7

The nucleotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 24. Only the amino acid sequence is shown in SEQ ID NO: 25.

5 Gene SCR-8

The gene is the same gene as *Mus musculus* mRNA for ADAM23 of a GenBank accession number AB009673.

10 The nucleotide sequence of the gene from mouse and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 26. Only the amino acid sequence is shown in SEQ ID NO: 27.

The sequence has a high homology with a sequence 15 described by JP 11155574-A and the sequence described by JP 11155574-A is considered to be a human ortholog.

The nucleotide sequence of the gene from human and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 28. Only the amino acid sequence is shown in SEQ ID NO: 29.

20 Polypeptides which are products of these genes have an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor 25 cells. The expression that a polypeptide has an activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor

cells means that proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells is supported in the presence of the polypeptide or in the presence of stroma cells expressing the 5 polypeptide.

Therefore, the present invention provides use of the polypeptides and DNAs encoding the polypeptides and novel polypeptides among the polypeptides and DNAs encoding the novel polypeptides.

10 A stem cell proliferation-supporting factor which is a polypeptide encoded by the DNA can be produced by introducing the DNA into a suitable host to prepare a transformant cell, and allowing the DNA to be expressed in the transformant cell.

15 The DNA may encode the above described factors which have amino acid sequences including substitution, deletion or insertion of one or several amino acids, as long as the activity of the stem cell proliferation-supporting factor to be encoded is not lost. DNAs

20 encoding substantially equivalent polypeptides to this stem cell proliferation-supporting factor can be obtained by modifying the nucleotide sequences so as to include substitution, deletion, insertion, addition, or inversion of amino acid residues in a specific region 25 using site-directed mutagenesis.

The DNAs including the above described mutation can be expressed in appropriate cells and the activity to

support hematopoietic stem cells, of the expressed products can be examined, so that the DNAs encoding the polypeptide having functions which are substantially equivalent to this stem cell proliferation-supporting 5 factor are obtained. In addition, the DNAs encoding substantially equivalently active protein as this stem cell proliferation-supporting factor can be obtained by isolating DNAs which hybridize with DNAs including, for example, the nucleotide sequence (ORF portion) as 10 described in SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, or 47 from the cells having the DNA, or probes prepared from these DNAs under the stringent condition; and which encode proteins possessing the activity to support hematopoietic stem cells. The 15 length of the probe is usually 30 to 1000 nucleotides. The stringent condition is, for example, one in which DNAs having homology (determinable with homology search in the compare function of DNASIS version 3.7 (Hitachi Software Engineering)) at not less than 70%, preferably 20 at not less than 80%, are hybridized each other and DNAs having less homology than those are not hybridized each other. The above described stringent condition may be 6 \times SSC, 5 \times Denhardt, 0.5% SDS, 68°C (SSC; 3 M NaCl, 0.3 M sodium citrate) (50 \times Denhardt; 1% BSA, 1% polyvinyl 25 pyrrolidone, 1% Ficoll 400) or 6 \times SSC, 5 \times Deanhardt, 0.5% SDS, 50% Formamide, 42°C, or the like.

Microorganisms such as *Escherichia coli* and yeast,

culture cells derived from animals or plants, and the like are used for host cells for expressing the DNA. Preferably, culture cells derived from mammals are used as the host cells. In the case that prokaryotic cells 5 are used as the host cells, the expression is preferably performed in a condition in which a signal peptide region is replaced with a leader sequence suitable for the prokaryotic cells such as β -lactamase (*bla*), alkaline phosphatase (*phoA*), and outer membrane protein 10 *A* (*ompA*) and the like, or in a form in which a methionine residue is added to the N-terminal site of the mature protein.

The introduction of the DNA to the host cell can be carried out by, for example, incorporating the DNA into 15 a vector suitable for the host in an expressible form, and introducing the resultant recombinant vector to the host cell.

Examples of the culture cells derived from mammals include CHO cell, 293 cell, COS7 cell, and the like. 20 Gene expression regulatory sequence such as a promoter to express the DNA may be originated from the gene itself, or may be derived from other genes such as cytomegalovirus promoter and elongation factor 1 promoter and the like.

25 Examples of a vector for animal culture cells include plasmid vectors, retrovirus vectors, adenovirus vectors (Neering, S.J., *Blood*, 88: 1147, 1996), herpes

virus vectors (Dilloo, D., *Blood*, 89: 119, 1997), HIV vectors, and the like.

In order to introduce the recombinant vector into culture cells, the conventional methods which are 5 usually employed for transformation of culture cells such as calcium phosphate transfection, the liposome method, the DEAE dextran method, the electroporation method and the microinjection method are employed.

The polypeptides of the present invention also 10 comprise polypeptides having amino acid sequences in which one or several amino acids are substituted, deleted or inserted in the amino acid sequence represented in SEQ ID NO: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27 or 29, and having activity to support 15 hematopoietic stem cells in addition to the polypeptides having the amino acid sequence represented in SEQ ID NO: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 48. That is, even if mouse and human stem cell proliferation-supporting factors are modified by substitution, 20 deletion, insertion or the like, polypeptides holding essential functions as a stem cell proliferation-supporting factor can be considered to be substantially equivalent to the stem cell proliferation-supporting factor.

25 These modified stem cell proliferation-supporting factors can be obtained by treating DNA encoding the stem cell proliferation-supporting factor or host cells

including the above mentioned DNA with a mutagen, or by mutating the above mentioned DNA so as to substitute, delete, or insert an amino acid at a specific site using site-directed mutagenesis. The residual of the activity

5 to support the hematopoietic stem cells in the obtained mutant polypeptide is confirmed by transferring hematopoietic stem cells cultured in the presence of the mutant polypeptides into irradiated mice, and monitoring peripheral hematological cellularity over time, as in

10 the examples described below.

As for the amino acid deletion, the polypeptide may be a fragment which lacks an amino acid sequence at the N-terminal end and/or the C-terminal end. The fragment lacking the amino acid sequence at the N-terminal end

15 and/or the C-terminal end can be obtained by a usual method, and the hematopoietic stem cell-supporting activity of the fragment can be determined by a similar way to that described with respect to the mutated polypeptide. In particular, if there is a portion

20 predicted as a signal sequence or a transmembrane region in the amino acid sequence, a fragment having the hematopoietic stem cell-supporting activity is predicted by using it as an index. For example, a protein encoded by human SCR-8 is a transmembrane protein of type I

25 passing through the membrane once, and it is therefore predicted that even if it made to be a soluble protein lacking the transmembrane region, it has the activity to

support to proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells. The transmembrane region can be predicted with a known program based on the amino acid sequence. For example,

5 if it is predicted with a program called PSORT II (available through the Internet, URL:

<http://psort.nibb.ac.jp/index.html>), the transmembrane

region is amino acids at positions 790 to 806 in SEQ ID NO: 29, and it is predicted that even if a fragment up

10 to position 789, the fragment has activity to support proliferation or survival of hematopoietic stem cells or hematopoietic progenitor cells.

Since the nucleotide sequences of the above described DNAs have been clarified by the present 15 invention, the DNAs can be also obtained by isolating the corresponding DNAs from mouse or human cDNA or chromosome DNA libraries using PCR in which the oligonucleotides prepared based on these nucleotide sequences are used as primers or using hybridization in 20 which the oligonucleotides prepared based on these nucleotide sequences are used as probes.

In order to complete the present invention, the DNAs of the present invention have been isolated from cDNA library of AGM-s3-A9 cells which are a mouse stromal 25 cell line having the activity to support the hematopoietic stem cells, using SBH (Sequencing By Hybridization) method (Drmanac, S., *Nat. Biotechnol.*, 16.

54, 1998; Drmanac, R., *Methods. Enzymol.*, 303, 165, 1999) as described below. The mouse stromal cell lines having the activity to support the hematopoietic stem cells can be obtained using the method disclosed in 5 W099/03980 or from Cell Bank of Institute of Physical and Chemical Research (RIKEN) or ATCC.

An outline of SBH method will be described below. Probes having eight or nine nucleotides whose sequences are different from each other are prepared. When the 10 nucleotide sequences corresponding to those of the probe exist in a targeted gene, the probes can hybridize with the gene. The hybridization can be easily detected with utilization of radio isotope- or fluorescence-labelled probes. Each clone in the library is picked up, and 15 blotted on a membrane. Then, the repeated hybridizations are performed with the each of above described probes, so that one can identify the combination of probes that hybridize to each clone. Since the combination of hybridized probes depends on 20 genes, the combination of probes which hybridize to an identical gene is the same. That is, the same gene can be identified as one group (cluster) according to the the combination of the hybridized probes. The number of clones of each gene in the cDNA library can be 25 determined by classifying each clone in the library based on patterns of the hybridized probes and counting the classified clones. Thus, frequency of expression of

each gene in the library can be determined.

CDNA libraries are prepared from cells having an activity to support the hematopoietic stem cells and from cells not having the activity. Clustering is

5 performed for the cDNA libraries. Statuses of expressed genes among cells are compared, so that the genes highly expressed with specificity to the supporting cells are selected. The expression statuses of these genes in each of above described cells are further examined by

10 Northern blot analysis, so that genes which are highly expressed in the cells having the activity to support the hematopoietic stem cells are obtained.

The above mentioned genes are the genes which are highly expressed with specificity to the supporting

15 cells and which are obtained through the above described process. Full-length genes have been cloned from the cDNA library derived from AGM-s3-A9 cell.

Further, in order to determine an ability of gene products to support hematopoiesis, a gene fragment

20 including gene ORF was transferred into stromal cells using a retrovirus vector, and the change in the activity to support the hematopoietic stem cells of the stromal cells was determined. Specifically, after the stromal cells into which the gene was not introduced or

25 into which a control vector was introduced and those into which the gene was introduced were each co-cultured with the mouse hematopoietic stem cells, the

hematopoietic cells were transplanted into irradiated mice. The engraftment of the co-cultured hematopoietic cells in recipient mice were examined. As a result, the mice into which the hematopoietic stem cells co-cultured 5 with the gene-introduced cells were transplanted, showed increased chimerism after the transplantation compared with co-culture with the cells into which the gene was not introduced. This result shows that in the gene-expressed stromal cells, an activity to support the 10 proliferation or survival of the hematopoietic stem cells or the hematopoietic progenitor cells is increased or imparted. As a result, it has become evident that expression of the above described genes has a function to increase the above described activity in the stromal 15 cells or impart the activity to the stromal cells. Therefore, it is revealed that products of the genes affect hematopoietic stem cells or hematopoietic progenitor cells to show an activity to support the survival or the proliferation thereof, or affect stromal 20 cells to show an activity to increase an activity to support the hematopoietic stem cells therein or impart the activity thereto.

The polypeptides of the present invention can be used as a medicine to proliferate or support human 25 hematopoietic stem cells or human hematopoietic progenitor cells when they affect hematopoietic stem cells or hematopoietic progenitor cells to show an

activity to support survival or proliferation thereof, in other words, the polypeptides have an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells if the

5 hematopoietic stem cells or the hematopoietic progenitor cells are cultured in the presence of the polypeptides. The pharmaceutical composition can be used for supporting proliferation or survival of human hematopoietic stem cells or human hematopoietic

10 progenitor cells *in vitro*. For hematopoietic stem cell transplantation therapies such as peripheral blood stem cell transplantation and cord blood stem cell transplantation, a sufficient amount of the hematopoietic stem cells sometimes cannot be collected

15 and the transplantation may not be performed. Even if the enough amount of the stem cells can not be collected, the enough amount of the hematopoietic stem cells can be obtained and transplanted by amplification of the hematopoietic stem cells *in vitro* using this

20 polypeptides. That is, the hematopoietic stem cells can be amplified without differentiation by culturing the hematopoietic stem cells in culture medium including these polypeptides. It may be considered the hematopoietic stem cells are able to be amplified more

25 efficiently with addition of a variety of cytokines to the medium.

When the hematopoietic stem cells or the

hematopoietic progenitor cells are cultured in the medium including the polypeptides of the present invention, the hematopoietic stem cells or the hematopoietic progenitor cells used may be isolated one 5 of these cell types alone or may be both of the cell types. In addition, the cells may include at least the hematopoietic stem cells or the hematopoietic progenitor cells, and include other hematopoietic cells. Further, it can be used a fraction containing hematopoietic stem 10 cells or progenitor cells fractionated from the cell population that contain the hematopoietic stem cells or progenitor cells.

Examples of sources of the hematopoietic stem cells and the hematopoietic progenitor cells in the method of 15 the present invention include a fetal liver, bone marrow, fetal bone marrow, peripheral blood, the peripheral blood from persons whose stem cells are mobilized by administration of cytokines and/or antitumor drugs, cord blood, and the like of mammals such as human and mouse 20 and the like. Any sources may be used as long as the tissue includes the hematopoietic stem cells.

A culture method using petri dishes and flasks for culture may be employed to culture the hematopoietic stem cells or the hematopoietic progenitor cells. The 25 cultivation of the hematopoietic stem cells and/or progenitor cells may be improved by mechanically controlling medium composition, pH, and the like, and

using a bioreactor capable of high density cultivation (Schwartz, *Proc. Natl. Acad. Sci. U.S.A.*, 88: 6760, 1991; Koller, M.R., *Bio/Technology*, 11: 358, 1993; Koller, M.R., *Blood*, 82: 378, 1993; Palsson, B.O., 5 *Bio/Technology*, 11: 368, 1993).

The stromal cells in which DNAs encoding the polypeptide of the present invention can be obtained as described with respect to the expression of the DNAs.

The co-culture of the stromal cells and the 10 hematopoietic cells can be performed simply after the collection of the bone marrow cells without further separation. Furthermore, co-culture can be performed by separating components such as stromal cells, hematopoietic cells and other cell populations from 15 collected bone marrow and combining them with the hematopoietic cells and stromal cells which are not from the individual from which the bone marrow is collected. Furthermore, after stromal cells are cultured to grow to 20 the stromal cells, hematopoietic cells can be added to perform co-culture with the hematopoietic stem cells. At this time, cell stimulating factors can be added to the culture system of stromal cells to more effectively support proliferation and survival. Concrete examples of the cell stimulating factor include a growth factor 25 which is typically a cytokine such as SCF (stem cell factor), IL-3 (interleukin 3), GM-CSF (granulocyte/macrophage colony-stimulating factor), IL-6

(interleukin 6), TPO (thrombopoietin), G-CSF (granulocyte colony-stimulating factor), TGF- β (transforming growth factor- β), MIP-1 α (Davatidis, G., J. Exp. Med. 167: 1939, 1988); a differentiation and 5 proliferation control factor such as hematopoietic hormones such as EPO (erythropoietin), chemokine, Wnt gene product, and notch ligand; and a development control factor.

In addition, when the polypeptide of the present 10 invention affects hematopoietic stem cells or hematopoietic progenitor cells to show an activity to support survival or proliferation thereof, in other words, the polypeptide has an activity to support survival or proliferation of hematopoietic stem cells or 15 hematopoietic progenitor cells if the hematopoietic stem cells or the hematopoietic progenitor cells are cultured in the presence of the polypeptide, the proliferation and the survival of the hematopoietic stem cells or the hematopoietic progenitor cells can be retained by 20 allowing the recombinant polypeptide of the present invention alone or in combination with the cell stimulating factors to affect hematopoietic stem cells or hematopoietic progenitor cells, without stromal cells. Examples of the cell stimulating factors used in this 25 case are above described cell stimulating factors and the like.

Medium used for the culture is not specially

restricted as long as the proliferation or the survival of the hematopoietic stem cells or the hematopoietic progenitor cells is not harmed. Preferable media are, for example, MEM- α medium (GIBCO BRL), SF-02 medium 5 (Sanko Junyaku), Opti-MEM medium (GIBCO BRL), IMDM medium (GIBCO BRL), and PRMI1640 medium (GIBCO BRL). A culture temperature is usually ranging from 25 to 39°C, and preferably ranging from 33 to 39°C. Examples of additives to the medium are fetal bovine serum, human 10 serum, horse serum, insulin, transferrin, lactoferrin, ethanolamine, sodium selenite, monothioglycerol, 2-mercaptopropanoic acid, bovine serum albumin, sodium pyruvate, polyethylene glycol, a variety of vitamins, and a variety of amino acids. A concentration of CO₂ is 15 usually ranging from four to six percent, and preferably five percent.

Since the hematopoietic stem cells can differentiate into all the hematopoietic cell lineages, the hematopoietic stem cells can be amplified and 20 differentiated into a specific cell type *in vitro*, and then the specific cells can be transplanted. For example, when erythrocytes are necessary, after the cultivation of the patient's stem cells to amplify them, the hematopoietic cells whose main component is the 25 erythrocyte can be artificially produced using an erythrocyte differentiation induction-promoting factor such as EPO.

The hematopoietic stem cells or the hematopoietic progenitor cells cultured using the polypeptides of the present invention can be used as a graft for blood cell transplantation replacing the conventional bone marrow transplantation or cord blood transplantation.

Transplantation of the hematopoietic stem cells is superior to the conventional blood cell transplantation therapy, since the engraftment can last semipermanently.

The transplantation of the hematopoietic stem cells can be employed as therapy for a variety of diseases in addition to combination therapy with total body X-ray irradiation therapy or advanced chemotherapy for leukemia. For example, when therapy accompanied with myelosuppression as an adverse reaction, such as chemotherapy, radiation therapy, and the like is performed for the patient with solid cancer, the patient can get benefit of early recovery and stronger chemotherapy than the conventional one can be performed to improve the therapeutic effect of the chemotherapy by collecting the bone marrow before the therapy, allowing the hematopoietic stem cells or the hematopoietic progenitor cells to be amplified *in vitro* and returning the amplified cells to the patient after the therapy.

In addition, by allowing the hematopoietic stem cells or the hematopoietic progenitor cells obtained according to the present invention to be differentiated into a variety of hematopoietic cells and transplanting these

.

cells into a patient with hypoplasia of a given hematopoietic cells, the patient's deficient status can be improved. In addition, this therapy can improve dyshemopoietic anemia to develop anemia such as aplastic 5 anemia caused by bone marrow hypoplasia. Furthermore, examples of diseases in which the transplantation of the hematopoietic stem cells according to the present invention is effective include immunodeficiency syndrome such as chronic granulomatous disease, duplicated 10 immunodeficiency syndrome, agammaglobulinemia, Wiskott-Aldrich syndrome, acquired immunodeficiency syndrome (AIDS), and the like, thalassemia, hemolytic anemia due to an enzyme defect, congenital anemia such as sickleemia, Gaucher's disease, lysosomal storage disease such as 15 mucopolysaccharidosis, adrenoleukodegeneracy, a variety of cancers and tumors, and the like.

Transplantation of the hematopoietic stem cells may be performed in the same manner as the conventional bone marrow transplantation or cord blood transplantation 20 other than the differences of the cells used.

The source of the hematopoietic stem cells which may be used for the above described hematopoietic stem cell transplantation is not restricted to the bone marrow, and the above described fetal liver, the fetal bone 25 marrow, the peripheral blood, the peripheral blood with stem cells mobilized by administration of cytokines and/or antitumor drugs, the cord blood, and the like may

be used.

The graft may be a composition including buffer solution and the like in addition to the hematopoietic stem cells and the hematopoietic progenitor cells 5 produced by the method according to the present invention.

The hematopoietic stem cells or the hematopoietic progenitor cells produced according to the present invention may be used for *ex vivo* gene therapy. Because 10 of the low frequency of recombination of target genes to the chromosome because the stem cells are in the resting state, differentiation of the stem cells during the culture period, and the like, the gene therapy to the hematopoietic stem cells has been hard to be established. 15 However, the present invention can amplify the stem cells without differentiation, so that efficacy of gene transfer is expected to be remarkably improved. In this gene therapy, a foreign gene (a gene for therapy) is transferred into the hematopoietic stem cells or the 20 hematopoietic progenitor cells, and then the obtained gene-transferred cells are used. The foreign gene to be transferred is appropriately selected according to disease. Examples of diseases in which the target cells of the gene therapy are the hematopoietic cells include 25 immunodeficiency syndrome such as chronic granulomatous disease, duplicated immunodeficiency syndrome, agammaglobulinemia, Wiskott-Aldrich syndrome, acquired

immunodeficiency syndrome (AIDS), and the like, thalassemia, hemolytic anemia due to an enzyme defect, congenital anemia such as sickleemia, Gaucher's disease, lysosomal storage disease such as mucopolysaccharidosis, 5 adrenoleukodegeneracy, a variety of cancers and tumors, and the like.

A usual method used for transfer of a gene into animal cells is employed for the transfer of the gene for the therapy into the hematopoietic stem cells or the 10 hematopoietic progenitor cells. Examples include a method using a vector for animal cells derived from virus utilized for a gene therapy such as retrovirus vectors such as Moloney mouse leukemia virus, adenovirus vectors, adeno-associated virus (AAV) vectors, herpes simplex virus vectors, and HIV vectors (with respect to a vector for gene therapy, see Verma, I.M., *Nature*, 389: 239, 1997); calcium phosphate transfection, DEAE-dextran transfection, electroporation, the liposome method, the lipofection method, the microinjection method, and the 15 like. Among them, the method using the retrovirus vector, the adeno-associated virus vector, or the HIV vector is preferable, since permanent expression of a gene is expected due to insertion into the chromosome DNA of a target cell.

20 25 For example, the adeno-associated virus (AAV) vector can be prepared as follows. First, a vector plasmid in which a gene for therapy is inserted into ITR (inverted

terminal repeat) at both ends of wild-type adeno-associated virus DNA and a helper plasmid for supplementing virus proteins are transfected into 293 cell line. Next, adenovirus as helper virus is infected, 5 so that virus particles including the AAV vector are produced. Alternatively, instead of adenovirus, a plasmid which expresses adenovirus gene having helper function may be transfected. The hematopoietic stem cells or the hematopoietic progenitor cells are infected 10 with the obtained virus particles. Preferably, appropriate promoter, enhancer, insulator and the like are inserted into the upstream region of the target gene in the vector DNA, so that the expression of the gene is regulated. When a marker gene such as a drug resistant 15 gene is used in addition to the gene for therapy, cells into which the gene for therapy are transferred are easily selected. The gene for therapy may be a sense gene or an antisense gene.

A composition for gene therapy may include a buffer 20 solution and a novel active ingredient and the like in addition to the hematopoietic stem cells or the hematopoietic progenitor cells by the method according to the present invention.

A vector for gene therapy can be produced by 25 incorporating the DNA of the present invention in an expression vector using a usual method. This vector for gene therapy is useful to treat diseases which need

survival and proliferation of the human hematopoietic stem cells. That is, the vector for gene therapy is transferred into the hematopoietic stem cells and the cells are cultured *in vitro*, so that the hematopoietic 5 stem cells or the hematopoietic progenitor cells can proliferate dominantly. The proliferation of hematopoietic stem cells *in vivo* can be caused by returning these hematopoietic stem cells thus treated. The proliferation of hematopoietic stem cells *in vivo* 10 can significantly be promoted by introducing this vector for gene therapy into the body. Alternatively, the bone marrow cells derived from a patient are cultured as it is and this vector for gene therapy is transferred thereto, so that the hematopoietic stem cells or the 15 hematopoietic progenitor cells can be proliferated in a culture system. Alternatively, this vector for gene therapy is transferred into the stromal cells and mesenchaymal stem cells obtained by isolating and culturing stromal cells from the bone marrow, so that 20 the activity to support the hematopoietic stem cells can be added or increased.

As shown in Examples, since it is possible that by introducing the DNA of the present invention into the stromal cells without the activity to support the 25 hematopoietic stem cells, this activity can be imparted, stromal cells having the activity to support the hematopoietic stem cells can be prepared by gene

transfer to stromal cells derived from human or mouse.

The stromal cells expressing the DNA of the present

invention and the hematopoietic stem cells or the

hematopoietic progenitor cells are co-cultured, so that

5 the hematopoietic stem cells or the hematopoietic
progenitor cells can survive and proliferate so as to be
useful for a variety treatment.

Since the hematopoietic stem cells or the

hematopoietic progenitor cells can survive and

10 proliferate by expression of the DNA of the present
invention in the stromal cell, an activity to support
the hematopoietic stem cells of the stromal cells can be
determined using the expression of the DNA of the
present invention as an index. The expression of the
15 DNA of the present invention in the stromal cells can be
confirmed using an antibody against a polypeptide
encoded by the DNA of the present invention. Also, PCR
primers can be prepared based on nucleotide sequences,
and RNA is prepared from the stromal cells of interest,
20 and RT-PCR is performed, so that the expression of the
DNA of the present invention can be confirmed. The
antibody will be described below.

The pharmaceutical composition of the present

invention can be administered to human. The

25 pharmaceutical composition having an activity to
proliferate or to support the human hematopoietic stem
cells or the hematopoietic progenitor cells can be

produced by mixing medically acceptable diluent, stabilizer, carrier, and/or other additives with the polypeptides of the present invention. At this time, in order to increase the stability of the protein *in vivo*,

5 the polypeptides of the present invention may be modified by a modifying agent. Examples of the modifying agent include polyethylene glycol (PEG), dextran, poly(N-vinyl-pyrrolidone), polypropylene glycol homopolymer, polypropylene oxide/ethylene oxide

10 copolymer, polyoxyethylated polyol, polyvinyl alcohol, and the like. The modification of the protein with PEG can be performed by, for example, a method in which activated ester derivatives of PEG is reacted with the protein, a method in which aldehyde derivatives at the

15 terminal portion of PEG is reacted with the protein in the presence of a reducing agent, and the like.

Japanese Patent Application Laid-Open No. 10-510980 discloses such protein modification in detail.

When the pharmaceutical composition of the present

20 invention is administered to human, recovery from hematological suppression due to an adverse drug reaction of carcinostatics; early recovery of hematopoietic cells at bone marrow transplantation, peripheral blood stem cell transplantation, or cord

25 blood transplantation; and recovery of hematopoietic function at pancytopenia such as aplastic anemia (AA) and myelodysplastic syndrome (MDS) are expected.

The antibodies of the present invention react specifically to the above described polypeptides of the present invention. The antibodies of the present invention may be monoclonal antibodies or polyclonal 5 antibodies as long as they react specifically to the above described polypeptides.

The antibodies of the present invention can be prepared according to usual methods. For example, the antibodies can be prepared either *in vivo* method in 10 which animals are additionally immunized by an antigen together with adjuvant once or several times at an interval of several weeks or *in vitro* method in which immune cells are isolated and sensitized in an appropriate culture system. Examples of immune cells 15 which can produce the antibodies of the present invention include splenic cells, tonsillar cells, lymph gland cells, and the like.

The whole polypeptide according to the present invention is not necessarily used as an antigen. A part 20 of this polypeptide may be used as an antigen. When the antigen is a short peptide, particularly, a peptide made of about 20 amino acid residues, it may be used by binding it to a carrier protein having high antigenicity such as keyhole limpet hemocyanin or bovine serum 25 albumin using chemical modification and the like. Alternatively, the antigen may be used by covalently binding it to peptide having branching skeleton such as

lysine core MAP peptide instead of the carrier protein (Posnett et al., *J. Biol. Chem.*, 263, 1719-1725, 1988; Lu et al., *Mol. Immunol.*, 28, 623-630, 1991; Briand et al., *J. Immunol. Methods*, 156, 255-265, 1992).

5 Examples of adjuvant include Freund's complete adjuvant, Freund's incomplete adjuvant, aluminum hydroxide gel, and the like. Antigen-given animals are, for example, mouse, rat, rabbit, sheep, goat, chicken, bovine, horse, guinea pig, hamster, and the like. The 10 blood is collected from these animals and the serum is separated. Then, immunoglobulin is purified from the serum using an ammonium sulfate precipitation method, anion exchange chromatography, protein A chromatography, or protein G chromatography to obtain polyclonal 15 antibodies.

With respect to chicken, antibodies can be purified from an egg. Monoclonal antibodies can be prepared by purification from supernatant of culture of hybridoma cells which are made by fusion of the immune cells 20 sensitized *in vitro*, or immune cells from the above described animals with parent cells capable of cultivation, or ascites from animals which received intraperitoneal administration of hybridoma cells.

Examples of parent cells include X63, NS-1, P3U1, 25 X63.653, SP2/0, Y3, SK0-007, GM1500, UC729-6, HM2.0, NP4-1 cell lines, and the like. Preparation may be performed by cultivating the immortalized antibody-

forming cells obtained by sensitization *in vitro*, or infection of a proper virus such as EB virus to the immune cells of the above described animals.

In addition to these cell engineering methods, the 5 antibodies can be obtained using gene engineering methods. For example, the antibody gene obtained from the *in vitro* sensitized cells or immune cells derived from the above described animals is amplified by PCR (polymerase chain reaction) and isolated, and the 10 amplified genes are transferred into microorganisms such as *E. coli* to produce the antibodies. Alternatively, the antibodies may be expressed on surfaces of phages as fused proteins.

By measuring polypeptides *in vivo* using the 15 antibodies of the present invention, the relationship between the polypeptides and pathological status of a variety of diseases can be clarified. Moreover, the antibodies can be used for diagnosis and treatment of diseases, and efficient affinity purification of the 20 polypeptides.

The present invention provides polypeptides having an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells by effecting thereon, or an activity to impart an 25 activity to support the hematopoietic stem cells to stromal cells by effecting thereon, and also provides DNAs encoding thereof. The polypeptides of the present

invention can efficiently maintain the proliferation or the survival of the hematopoietic stem cells or the hematopoietic progenitor cells.

5 Best Mode for Carrying out the Invention

Hereafter, the present invention will be described in detail by reference to examples.

Example 1 Preparation of fragment of gene which is

10 specifically expressed in hematopoietic stem cell-
 supporting cells

(I) Preparation of stromal cell line derived from mouse
AGM

(1) Isolation of AGM region from fetal mouse

15 C3H/HeNSLc mice of both genders (purchased from
Japan SLC INC.) were kept under a SPF (specific
pathogen-free) environment. One or two female mice and
one male mouse were placed in the same cage over a night.

20 In the next morning, the female mice in which the
existence of a vaginal plug was observed were
transferred to other cages and kept. The day when the
existence of the vaginal plug was observed was defined
to be the 0.5th day of pregnancy. On the 10.5th day of
the pregnancy, after mouse was sacrificed by cervical
25 dislocation, fetuses were extirpated. Isolation of AGM
regions was performed according to the method by Godin
et al. (Godin, I., *Proc. Natl. Acad. Sci. U.S.A.*, 92:

773-777, 1995) and the method by Medvinsky et al. (Medvinsky, A.L., *Blood*, 87: 557-565, 1996). The fetuses were placed in a culture dishes to which PBS(-) (phosphate buffered saline) (produced by Nissui Seiyaku) 5 was added in a volume just sufficient to cover the fetuses. After the AGM regions were carefully excised so as not to include other regions under a stereoscopic microscope, they were put in another 24-well culture dish (Nunc).

10 10 (2) Establishment of cell lines derived from AGM One drop of MEM medium (Sigma) containing 10% FCS (Hyclone) was added to the AGM regions in the 24-well culture dish (Nunc), and AGM regions were cultured in an incubator overnight. The culture was performed in the 15 MEM medium (Sigma) containing 10% FCS (Hyclone) at 37°C, in an atmosphere of 5% CO₂, and at a humidity of 100%. When the cells of the AGM regions adhered to the culture dish due to overnight cultivation, two milliliters of MEM medium containing 10% FCS was further added.

20 20 Stromal cells began to appear around the AGM region tissue fragment after the continuous cultivation. After one-week cultivation, adhesive cells were separated by trypsin treatment (0.05% trypsin in PBS containing 0.53 mM EDTA (Gibco BRL) at 37°C for three to five minutes).

25 25 The stromal cells were then washed twice with the medium, and seeded on 6-well culture dish (Nunc). On the next day, the cells which did not adhere to the culture dish

and the medium were removed, and then, fresh medium was added. Two weeks after transfer to the 6-well culture dish, cells were γ -ray-irradiated at 900 Rad to eliminate endogenous hematopoietic cells. An attempt of 5 the direct cell cloning by limiting dilution from this culture system was made, but no cell proliferation was observed and the cloning ended in failure. Then, after the number of seeded cells in one well was increased and cells were adapted so as to be able to proliferate from 10 a small number of cells, the cells were cloned by limiting dilution.

Specifically, the AGM was extirpated and cultured in the same manner as described above. The culture system two weeks after the γ -ray radiation was trypsinized 15 (0.05% trypsin in PBS containing 0.53 mM EDTA at 37°C for three to five minutes) to suspend the cells, and the cells were seeded in a 24-well culture dish at 50 to 100 cells/well. After the culture was continued for three weeks, the cells were seeded in a 96-well culture dish 20 (Nunc) by means of limiting dilution, at 0.3 cells/well. The cells which were grown from the well in which only one cell was seeded were allowed to enlarge culture. As a result, the cells were successfully cloned to obtain fibroblast-like cells and cobble stone-like cells. 25 A CD34-positive cell fraction derived from the human cord blood was co-cultured with the fibroblast-like cells for two weeks to examine the presence of colony-

forming cells during the culture. Colony-forming cells could not be found in the co-culture system with the fibroblast-like cells. Then, the similar examination was performed for seven cell clones showing the cobblestone-like form. Three clones having an activity to support proliferation of human hematopoietic stem cells were obtained and were named AGM-s1, AGM-s2, and AGM-s3.

5 (II) Preparation of hematopoietic stem cells from mouse bone marrow

10 Bone marrow was collected from a femur of C57BL/6-Ly5.1 pep (eight- to ten-week age, and male) (the gift from Professor K. Nakauchi, University of Tsukuba), and suspended in PBS. After the mouse bone marrow mononuclear cells were concentrated by specific gravity

15 centrifugation according to the usual method (S. Kouzu, Fundamental techniques for immunology, YODOSHA, 1995), the cells were suspended in staining buffer (PBS containing 5% FCS and 0.05% NaN_3), and a hematopoietic stem cell fraction was obtained as follows (Osawa, M. et

20 al., Science 273: 242-245, 1996).

An FITC-conjugated anti-CD34 antibody, a phycoerythrin-conjugated anti-Sca-1 antibody, an allophycocyanin anti-c-Kit antibody (all purchased from Pharmingen) and six biotylated anti-differentiation

25 antigen antibodies (CD45R, CD4, CD8, Gr-1, Ter119, and CD11c, all purchased from Pharmingen) as molecular markers (Lin), were added to a suspension of the bone

marrow mononuclear cells and incubated for 20 min on ice to cause reaction. After the cells were washed twice with staining buffer, CD34-negative, Sca-1-positive, c-Kit-positive, and Lin-negative cells were isolated on a 5 cell sorter (FACS Vantage, Becton Dickinson).

(III) Subcloning of mouse stromal cell line and determination of activity to support hematopoietic stem cells of a variety of cell lines

(1) Subcloning of mouse stromal cell line

10 1) Isolation of AGM-s3 subclone

Stromal cell line AGM-s3 derived from AGM, which was subcultured in MEM α medium (GIBCO BRL) including inactivated 10% FCS (bovine fetal serum, Hyclone), was suspended in PBS containing 5% FCS (PBS-FCS). Clone 15 sorting was performed in a 96-well culture dish (Falcon) at one cell/well using a cell sorter (FACS Vantage; Becton Dickinson). Among cells in the 96 wells, cultures of the cells which grew were expanded, so that thirteen kinds of AGM-s3 subclones were obtained. The 20 activity to support the hematopoietic cells of these AGM-s3 subclones were examined.

2) Isolation of human cord blood CD34-positive stem cell

The human cord blood was collected at normal delivery according to the criteria approved by Ethics 25 committee of Kirin Beer Iyaku Tansaku Kenkyusho. The cord blood was collected using a heparin-added syringe so as not to coagulate. The heparin treated cord blood

was overlaid on Lymphoprep (NYCOMED PHARMA), and mononuclear cells were separated by specific gravity centrifugation (at 400G, at room temperature, and for 30 minutes). Erythrocytes contaminated in the mononuclear cell fraction were lysed by treatment with an ammonium chloride buffer solution (0.83% NH₄Cl-Tris HCl, 20 mM, pH 6.8) at room temperature for two minutes. After the mononuclear cells were washed with PBS-FCS, ten milligrams of human IgG was added thereto and the mixture was allowed to stand on ice for ten minutes. Then, the cells were further washed with PBS-FCS. Biotinylated antibodies against the antigens specific to the human differentiated blood cells, that is, the antibodies against CD2, CD11c (purified from ATCC hybridoma), CD19 (Pharmingen), CD15, and CD41 (Leinco Technologies Inc.), and Glycophorin A (Cosmo Bio) were added thereto, and the mixture was allowed to stand on ice for 20 min. After washing with PBS-FCS, the cells were suspended in one milliliter of PBS containing 5% FCS, 10 mM EDTA, and 0.05% NaN₃ (PBS-FCS-EDTA-NaN₃). Streptavidin-bound magnetic beads (BioMag. Per Septive Diagnostics) were added thereto, and the mixture was allowed to stand on ice for 40 min. The differentiated blood cells which expressed differentiation antigens were removed using a magnetic separator (Dynal MPC-1 Dynal). An FITC-labeled anti-CD34 antibody (Immunotech S.A., Marseilles, France) was added to the remaining

differentiated blood cell antigen-negative cell fraction.

After incubation on ice for 20 min., a CD34-positive fraction was recovered using a cell sorter. This cell population was defined as a hematopoietic stem cell

5 population derived from the human cord blood.

3) Co-culture of the human hematopoietic stem cells and AGM-s3 subclone

After 13 kinds of AGM-s3 subclones and stromal cell line MS-5 derived from the mouse bone marrow were each 10 seeded in a 24-well culture dish (Falcon) at 1×10^4 cells/well, and cells were cultured in one milliliter of MEM α medium containing 10% FCS and allowed to grow until the cells covered all over the bottom surfaces of the wells. CD34-positive hematopoietic stem cells derived 15 from the human cord blood were placed on the above described stromal cells at 500 cells/well, and co-cultured in one milliliter of MEM α medium containing 10% FCS. One week after the start of the co-culture, one milliliter of the same medium was further added. Two 20 weeks after the start of the co-culture, the stromal cells and the human blood cells were trypsinized (0.05% trypsin in PBS containing 0.5 mM EDTA (GIBCO BRL) at 37°C; standing for two to five min.) to simultaneously separate them from the culture dish. An activity to 25 support the hematopoietic stem cells was determined with a clonogenic assay.

4) Assessment of proliferation statuses of the

hematopoietic stem cells and hematopoietic progenitor cells by clonogenic assay

The cells which proliferated in the above described co-culture system were appropriately diluted, and

5 subjected to one milliliter of methylcellulose culture system to be analyzed. The analysis using the methylcellulose culture system was performed using a 6-well culture dish (Falcon) in MethoCult H4230 (Stem Cell Technologies Inc.) to which 10 ng/ml of human SCF, human

10 IL-3, human IL-6, human G-CSF, and human TPO, and 2 IU/ml of EPO were added. All of a variety of the above described hematopoietic factors were recombinants and pure. After two-week culture, developed colonies were observed under a microscope to count numbers of CFU-GM

15 (granulocyte-macrophage colony-forming unit), BFU-E (erythroid burst forming unit), and CFU-E mix (erythrocyte mixed colony-forming unit).

Fig. 1 shows the result of two-week co-culture of the CD34-positive hematopoietic stem cells and the AGM-s3 subclone A9, A7, or D11. As a result of the co-culture, A9 and D11 subclones among 13 kinds of AGM-s3 subclones supported proliferation of all three series of CFU-GM, BFU-E, and CFU-E mix. Especially, although BFU-E and CFU-E mix, that is, the progenitor cells of erythrocytes were hardly to be supported in usual, their proliferations were observed in the co-culture system with A9 or D11 cells. The results showed that

proliferation or maintenance of the hematopoietic stem cells or the hematopoietic progenitor cells occurred in the co-culture with A9 or D11 cells and the progenitor cells of the erythrocyte were continuously supplied. In 5 contrast, although cellular morphology of A7 was similar to that of A9, A7 did not support CFU-GM, BFU-E, and CFU-E mix.

5) Comparison of an activity to support the human hematopoietic stem cells between A9 and a stromal cell 10 line OP9 derived from mouse fetus

Comparison of an activity to support the CD34-positive hematopoietic stem cells derived from the human cord blood between AGM-s3 subclones A9 and A7, and a stromal cell line OP9 derived from mouse fetus (RCB1124, 15 the Cell Development Bank of RIKEN) were performed with CFU-GM, BFU-E, CFU-E and CFU-E mix as indexes, using the above described determination system. Fig. 2 shows the result of the two-week co-culture. In the A7 cell culture system, CFU-GM, BFU-E, and CFU-E were 20 significantly decreased and CFU-E mix was completely disappeared. In contrast, with OP9 cells, a variety of blood cell progenitor cells including CFU-E mix were supported, although the supporting ability was less than that of A9 cells. Therefore, it has been found that OP9 25 cells possess the activity to support the hematopoietic stem cells.

(2) Assessment of activity to support the hematopoietic

stem cells in a variety of cell lines

The above described stromal cell lines (AGM-s3-A9, AGM-s3-A7, and AGM-s3-G1), 3T3Swiss (ATCC), OP9, and NIH3T3 (ATCC) were seeded in a 24-well culture dish 5 (Falcon) at 5×10^4 cells/well. The cell lines were cultured in MEM α medium (GIBCO BRL) containing inactivated 10% FCS (bovine fetal serum, Hyclone) for one day and allowed to proliferate until the cells covered all over the bottom surfaces of the wells. Then, 10 the medium was replaced to one milliliter of fresh medium, thirty cells of the mouse hematopoietic stem cells (derived from C57BL/6-Ly5.1) obtained in the above (II) were placed on this cell layer, and co-culture was started.

15 On seventh day of the cultivation, the cells were trypsinized (0.05% trypsin in PBS containing 0.5 mM EDTA (GIBCO BRL) at 37°C for two to five minutes) to separate and recover all the cells on the culture dish. The recovered whole cells of each cell line and 200,000 20 cells of whole bone marrow cells (derived from C57BL/6-Ly5.2 mouse, Charles River) were transplanted into C57BL/6-Ly5.2 mice (eight weeks age and male, Charles River) irradiated with X-ray at 8.5 Gy through the tail vein. After the transplantation, peripheral blood was 25 collected from orbit at intervals, and the ratio in number of cells derived from the C57BL/6-Ly5.1 prep mouse was determined with FACS. The peripheral blood

was analyzed according to the usual method (S. Kouzu, Fundamental techniques for immunology, YODOSHA, 1995). Three hundreds and fifty μ L of distilled water was added to 50 μ L of the peripheral blood, and the mixture was 5 allowed to stand for 30 seconds so as to lyze the erythrocytes. Then, PBS at twice concentrations was added and the mixture was centrifuged to recover white blood cells. After the cells were washed once using the staining buffer (PBS containing 5% FCS and 0.05% NaN_3), 10 anti-CD16 antibody, anti-Ly5.1 (CD45.1) antibody labeled with FITC, anti-Gr-1 and anti-CD11c antibodies labeled with phycoerythrin, and anti-CD45R (B220) and anti-CD90 (Thy1) antibodies labeled with allophycocyanin (all of these were purchased from Pharmingen) were added. After 15 these cells were allowed to stand for reaction in the ice bath for 30 minites, they were washed with the staining buffer and FACS analysis was performed.

Change in the number of cells capable of reconstitution during the hematopoietic stem cell 20 culture was determined by calculating the proportions of Ly5.1-positive cells in the Gr-1- or CD11c-positive cells (myeloid cells) and Ly5.1-positive cells in the CD90- or CD45R-positive cells (lymphoid cells) in the peripheral blood at intervals after transplantation. 25 Fig. 3 shows the results. When the cells were co-cultured with AGM-s3-A9 cells, OP9 cells, or 3T3Swiss cells, high chimerism of donor cells were maintained

after the transplantation. Therefore, these stromal cells were considered to have a high activity to support the hematopoietic stem cells. In contrast, when the cells were co-cultured with AGM-s3-A7 cells, AGM-s3-G1 5 cells, or NIH3T3 cells, high chimerism derived from the transplanted cells was not observed. Therefore, these stromal cells were low in an activity to support the hematopoietic stem cells or the hematopoietic progenitor cells.

10 (IV) Identification of sequences of genes which specifically express in hematopoietic stem cell-supporting cells

AGM-s3-A9 cells, AGM-s3-A7 cells and OP9 cells were each dissolved in 20 mL of ISOGEN (Nippon gene, Japan) 15 and total RNAs were prepared according to the attachment. Messenger RNAs were prepared from one milligram of the total RNAs according to the protocol of the mRNA purification kit (Amersham Pharmacia, U.S.A.). cDNAs were synthesized from the mRNAs and cDNA libraries 20 (hereinafter, also called as AGM-s3-A9 cDNA, AGM-s3-A7 cDNA and OP9 cDNA, respectively) were constructed using pSPORT1 (GIBCO Lifetech, U.S.A.). A clone harboring a cDNA fragment which highly expresses specifically to AGM-s3-A9 cells or OP9 cells compared with AGM-s3-A7 25 cells was obtained from the libraries with SBH method (Hyseq, U.S.A.). A nucleotide sequence of the obtained clone was determined using ABI377 DNA sequencer (Perkin

Elmer, U.S.A.).

As a result, it has been found that expression of genes comprising nucleotide sequences shown in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, 5 SEQ ID NO:6, and SEQ ID NO:7, or parts thereof in AGM-s3-A9 or OP9 cells is higher than that in AGM-s3-A7 cells. These genes were named as SCR-2, SCR-3, SCR-4, SCR-5, SCR-6, SCR-7 and SCR-8, respectively.

10 Example 2 Cloning of SCR-2 and activity determination

By searching GenBank database for the nucleotide sequence shown in SEQ ID NO: 1 with BLAST, it has been found that SCR-2 is the same gene as a mouse gene, *Mus musculus* glypican-1 (GPC-1) of an accession number 15 AF185613. The nucleotide sequence of ORF (Open Reading Frame) of SCR-2 and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 8. Only the amino acid sequence is shown in SEQ ID NO: 9.

The human nucleotide sequence of GPC-1 is recorded 20 in GenBank database under an accession number AX020122. The nucleotide sequence of ORF of AX020122 and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 10. Only the amino acid sequence is shown in SEQ ID NO: 11.

25 Determination of the activity to support the hematopoietic stem cells or hematopoietic progenitor cells was performed as follows.

(1) Construction of retrovirus vector for expression of mouse SCR-2

Based on the nucleotide sequence of SCR-2 ORF, SCR-2Fsall and SCR-2Reco primers having the following 5 nucleotide sequences were prepared, and PCR was performed using OP9 cDNA as a template.

SCR-2Fsall

CCGGTCGACCACCatggaactccggacccgaggctgg (SEQ ID NO: 30)

SCR-2Reco

10 CCGAATTCTtaccgccacctgggcctggctgc (SEQ ID NO: 31)

An amplified fragment was digested with restriction enzymes *Eco*RI and *Sal*I. After electrophoresis, a DNA fragment was purified using JETSORB (Genomed, Germany). The purified DNA fragment was ligated with pMX-IRES-GFP 15 vector digested with *Eco*RI and *Xba*I (gift from Professor T. Kitamura, TOKYO UNIV. INST. OF MEDICAL SCIENCE, Japan). The pMX-IRES-GFP vector is a plasmid obtained by inserting sequences encoding IRES (Internal Ribosome Entry Site) and GFP (Green Fluorescence Protein) into 20 the retrovirus vector pMX. IRES enables ribosome to access to the middle of the mRNA. Therefore, two genes can be expressed from one mRNA by ligation of upward and downward genes separated by IRES in one transcription unit during the construction of an expression vector. 25 With respect to the above-described plasmid, SCR-2 cDNA was inserted in the upward site and GFP (Green Fluorescence Protein) was inserted in the downward site.

Thus, the expression of SCR-2 could be monitored by detecting the expression status of GFP using FACS.

The obtained recombinant vector was introduced into *E. coli* DH5 α , and was seeded on LB agar medium 5 containing 100 μ g/ml of ampicillin, so that independent colonies were formed. After the isolated colony was cultured in 100 mL of LB medium containing 100 μ g/ml of ampicillin, plasmid was purified using QIAGENtip100 (QIAGEN, U.S.A.). The sequence of the inserted gene was 10 determined using a conventional method, so that the sequence was confirmed to be identical to the nucleotide sequence of SCR-2 ORF.

(2) Preparation of stromal cells highly expressing SCR-2 BOSC23 cells were seeded on a collagen type I-coated 15 60-mm dish (Asahi technoglass) at 2×10^6 cells/dish, and cultured in DMEM medium (GIBCO BRL) containing 10% FCS at 37°C, under an atmosphere of 5% CO₂, and at a humidity of 100%. Twelve to 18 hours after the start of the culture, the medium was replaced by two milliliters 20 of OPTI MEM medium (GIBCO BRL).

About 3 μ g of plasmid obtained by inserting SCR-2 into the above described pMX-IRES-GFP was added to 18 μ l of LIPOFECTAMINE Reagent (GIBCO BRL) diluted with 100 μ l of OPTI MEM medium, and the mixture was allowed to stand 25 at room temperature for 30 min. The prepared DNA solution was added to the prepared BOSC23 cell culture solution. After about five hours, two milliliters of

DMEM medium containing 20% FCS (GIBCO BRL) was added.

After about 24 hours, the medium was replaced by 4 ml of DMEM containing 10% FCS. Further, after about 48 hours, the culture medium was harvested. After the 5 culture medium was filtrated through 0.45- μ m filter, the filtrate was centrifuged at 1,200g for 16 hours and the supernatant was removed to obtain the virus precipitation.

AGM-s3-A7 or AGM-s3-A9 cells were cultured in one 10 milliliter of MEM α medium containing 10% FCS (GIBCO BRL) on a 24-well culture dish (FALCON) at 1×10^4 cells/well. After 12 to 18 hours, the virus precipitation was suspended in one milliliter of MEM α medium containing 10% FCS, and the stromal cell culture medium was 15 replaced by the virus suspension. Next, POLYBRENE (Sigma, SEQUA-BRENE) was added to be 10 μ g/ml. After the culture dish was centrifuged at 700g for 45 minutes, the cells were cultured at 37°C, under an atmosphere of 5% CO₂, and at a humidity of 100%. After 48 hours, the 20 medium was replaced by one milliliter of MEM α medium containing 10% FCS. After 24 hours, the cells were subcultured on a 6-well culture dish (FALCON) and cultured in three milliliters of MEM α medium containing 10% FCS. Forty-eight hours after the subculturing, GFP 25 expression in the stromal cells was detected using a cell sorter (FACSVantage, Becton Dickinson) to indirectly confirm that not less than 80% of cells

expressed SCR-2.

Also, the same procedures were repeated by using pMX-IRES-GFP vector instead of the plasmid obtained by inserting SCR-2 into pMX-IRES-GFP to prepare stromal 5 cells into which a control vector was introduced.

(3) Co-culture of human hematopoietic stem cells and stromal cells highly expressing SCR-2, and determination of proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells by clonogenic assay

10 In the same manner as described in (III) (1) 3) to 4) of Example 1, AGM-s3-A9 or AGM-s3-A7 cells in which SCR-2 was highly expressed through retrovirus, AGM-s3-A9 or AGM-s3-A7 cells into which a control vector was introduced, or AGM-s3-A9 or AGM-s3-A7 cells were co- 15 cultured with CD34-positive hematopoietic stem cells derived from human cord blood, and proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells are determined.

Fig. 4 shows results when the CD34-positive 20 hematopoietic stem cells were co-cultured with AGM-S3-A9 cells in which SCR-2 was highly expressed (A9/SCR-2), AGM-S3-A9 cells into which a control vector was introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks. Also, Fig. 5 shows results when the CD34- 25 positive hematopoietic stem cells were co-cultured with AGM-S3-A7 cells in which SCR-2 was highly expressed, AGM-S3-A7 cells into which a control vector was

introduced or AGM-S3-A7 cells for two weeks. As a result, by the co-culture with AGM-S3-A9 cells in which SCR-2 was highly expressed or AGM-S3-A7 cells in which SCR-2 was highly expressed, increases of BFU-E and CFU-C 5 were observed. Therefore, it has been revealed that the activity to support hematopoietic stem cells or hematopoietic progenitor cells, of AGM-S3-A9 or AGM-S3-A7 increases by allowing SCR-2 to be highly expressed. From the results, it has been revealed that a gene 10 product of SCR-2 has an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells or an activity to affect stromal cells to enhance a hematopoietic cell-supporting activity of the stromal cells or impart the activity to 15 the stromal cells.

Example 3 Cloning of SCR-3 and activity determination

By searching GenBank database for the nucleotide sequence shown in SEQ ID NO: 2 with BLAST, it has been 20 found that SCR-3 is the same gene as mouse genes, *Mus musculus* chemokine MMRP2 mRNA of an accession number U15209, *Mus musculus* C10-like chemokine mRNA of U19482 and mouse macrophage inflammatory protein-1gamma mRNA of U49513. The nucleotide sequence of SCR-3 ORF and the 25 amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 12. Only the amino acid sequence is shown in SEQ ID NO: 13.

Determination of the activity of SCR-3 to support the hematopoietic stem cells or hematopoietic progenitor cells was performed as follows.

(1) Construction of retrovirus vector for expression of
5 mouse SCR-3

Based on the nucleotide sequence of SCR-3 ORF, SCR-3FxhoI and SCR-3Reco primers having the following nucleotide sequences were prepared, and PCR was performed using AGM-s3-A9 cDNA as a template. An
10 amplified fragment was inserted to the retrovirus vector pMX-IRES-GFP in the same manner as described in (1) of Example 2.

SCR-3FxhoI

ccgCTCGAGccaccATGAAGCCTTTCATCTGCC (SEQ ID NO: 32)

15 SCR-3Reco

tccGAATTCTtattgttgttaggtccgtgg (SEQ ID NO: 33)

(2) Preparation of stromal cells highly expressing SCR-3
AGM-s3-A7 cells in which SCR-3 was highly expressed
20 were prepared by using the above retrovirus vector in
the same manner as (2) of Example 2.

(3) Determination of activity to support hematopoietic
stem cells of stromal cells in which SCR-3 is highly
expressed

25 In the same manner as described in (III) (2) of
Example 1, determination of the activity to support
hematopoietic stem cells was performed except that AGM-

S3-A7 cells, AGM-S3-A7 cells in which SCR-3 was highly expressed through retrovirus, and AGM-S3-A7 cells into which a control vector was introduced were seeded in a 24-well culture dish (Falcon) at 1×10^5 cells/well.

5 The results are shown in Fig. 6. Hematopoietic cells co-cultured with AGM-S3-A7 cells in which SCR-3 was highly expressed (A7/SCR-3) showed high chimerism in recipient individuals after the transplantation compared with the parent cell lines or hematopoietic cells co-
10 cultured with the cells into which a control vector was introduced. The high chimerism was observed in myeloid and lymphoid cells two months after the transplantation. Therefore, it is revealed that hematopoietic stem cells and hematopoietic progenitor cells which can
15 reconstitute the hematopoietic system in bodies of irradiated mice have maintained and amplified superiorly to the co-culture with cells into which SCR-3 is not introduced, during the co-culture period. From the results, it is revealed that an activity of stromal
20 cells to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells is increased by high expression of SCR-3. Therefore, it is revealed that a gene product of SCR-3 has an activity to affect hematopoietic stem cells or
25 hematopoietic progenitor cells to support survival or proliferation thereof or an activity to affect stromal cells to enhance a hematopoietic cell-supporting

activity of the stromal cells or impart the activity to the stromal cells.

Example 4 Cloning of SCR-4 and activity determination

5 By searching GenBank database for the nucleotide sequence shown in SEQ ID NO: 3 with BLAST, it has been found that SCR-4 has a high homology to *Homo sapiens* clone 25077 mRNA of an accession number AF131820, and that SCR-4 is a mouse ortholog. This sequence is
10 described in WO 00/66784.

The nucleotide sequence of ORF of AF131820 and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 16. Only the amino acid sequence is shown in SEQ ID NO: 17.

15 The nucleotide sequence of ORF of SCR-4 and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 14. Only the amino acid sequence is shown in SEQ ID NO: 15.

Determination of the activity of SCR-4 to support
20 the hematopoietic stem cells or hematopoietic progenitor cells was performed as follows.

(1) Construction of retrovirus vector for expression of human SCR-4

From 3 µg of mRNA derived from fetal liver (CLONETEC, 25 U.S.A.), cDNA was synthesized by using oligo-dT primer and reverse transcriptase (SuperscriptII, GIBCO-BRL). Using the cDNA as a template, the ORF region of human

SCR-4 was amplified by PCR with HSCR-4FxhoI and HSCR-4RecoRV primers having the following nucleotide sequences. An amplified fragment was digested with *Xho*I and inserted to the retrovirus vector pMX-IRES-GFP in 5 the same manner as described in (1) of Example 2. For the insertion, the pMX-IRES-GFP was digested with a restriction enzyme *Eco*RI, blunt-ended with KOD DNA synthase (TOYOB0, Japan) and digested with a restriction enzyme *Xho*I.

10 HSCR-4FxhoI

CCGCTCGAGCCACCatgttgtggctgcaaggctggtgt (SEQ ID NO: 34)

HSCR-4RecoRV

CCGGATATCtcatttcttctgttgccctcca (SEQ ID NO: 35)

15 (2) Preparation of stromal cells highly expressing human SCR-4

AGM-s3-A9 cells in which human SCR-4 was highly expressed were prepared by using the above retrovirus vector in the same manner as (2) of Example 2.

20 (3) Co-culture of human hematopoietic stem cells and stromal cells highly expressing human SCR-4, and determination of proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells by clonogenic assay

25 In the same manner as described in (III) (1) 3) to 4) of Example 1, AGM-s3-A9 cells in which SCR-4 was highly expressed through retrovirus, AGM-s3-A9 cells

into which a control vector was introduced, or AGM-s3-A9 cells were co-cultured with CD34-positive hematopoietic stem cells derived from human cord blood, and proliferation statuses of hematopoietic stem cells and 5 hematopoietic progenitor cells are determined.

Fig. 6 shows results when the CD34-positive hematopoietic stem cells were co-cultured with AGM-S3-A9 cells in which human SCR-4 was highly expressed, AGM-S3-A9 cells into which a control vector was introduced or 10 AGM-S3-A9 cells for two weeks. As a result, the co-culture with AGM-S3-A9 cells in which human SCR-4 was highly expressed, increases of BFU-E and CFU-C were observed. Therefore, it has been revealed that the activity to support hematopoietic stem cells or 15 hematopoietic progenitor cells, of AGM-S3-A9 increases by allowing human SCR-4 to be highly expressed. From the results, it has been revealed that human SCR-4 has an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor 20 cells or an activity to affect stromal cells to impart a hematopoietic cell-supporting activity to the stromal cells.

Example 5 Cloning of SCR-5 and activity determination

25 In the nucleotide sequence of SEQ ID NO: 4 obtained by the SBH analysis, the presence of ORF was predicted. The nucleotide sequence of ORF and the amino acid

sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 18. Only the amino acid sequence is shown in SEQ ID NO: 19.

By searching GenBank database for the nucleotide 5 sequence of SEQ ID NO: 18 with BLAST, it has been found that SCR-5 has a high homology with *Homo sapiens* esophageal cancer related gene 4 portein (ECRG4) mRNA of an accession number AF325503, and that SCR-5 is a mouse 10 ortholog of AF325503. The nuclotide sequence of ORF of AF325503 and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 20. Only 15 the amino acid sequence is shown in SEQ ID NO: 21.

Determination of the activity of SCR-5 to support the hematopoietic stem cells or hematopoietic progenitor 15 cells was performed as follows.

(1) Construction of retrovirus vector for expression of mouse SCR-5

Based on the nucleotide sequence of SCR-5 ORF, SCR-5FxhoI and SCR-5Rblunt primers having the following 20 nucleotide sequences were prepared for retrovirus cloning, and PCR was performed using DNA having the nucleotide sequence shown in SEQ ID NO: 23 as a template. An amplified fragment was digested with a restriction enzyme *Xho*I and inserted to the retrovirus vector pMX- 25 IRES-GFP in the same manner as described in (1) of Example 2. For the insertion, the pMX-IRES-GFP was digested with a restriction enzyme *Eco*RI, blunt-ended

with KOD DNA synthase (TOYOB0, Japan) and digested with a restriction enzyme *Xba*I.

SCR-5FxhoI

ccgCTCGAGccaccatgagcacctcgctgcgcg (SEQ ID NO: 36)

5 SCR-5Rblunt

tccGTTAACttaatagtcatcatagttca (SEQ ID NO: 37)

(2) Preparation of stromal cells highly expressing SCR-5 AGM-s3-A7 cells in which SCR-5 was highly expressed

10 were prepared by using the above retrovirus vector in the same manner as (2) of Example 2.

(3) Determination of activity to support hematopoietic stem cells of stromal cells in which SCR-5 is highly expressed

15 In the same manner as described in (3) of Example 3, determination of the activity to support hematopoietic stem cells was performed.

The results are shown in Fig. 8. Hematopoietic cells co-cultured with AGM-s3-A7 cells in which SCR-5 was highly expressed (A7/SCR-5) showed high chimerism in recipient individuals after the transplantation compared with the parent cell lines or hematopoietic cells co-cultured with the cells into which a control vector was introduced. The high chimerism was observed in myeloid and lymphoid cells two months after the transplantation. Therefore, it is revealed that hematopoietic stem cells and hematopoietic progenitor cells which can

reconstitute the hematopoietic system in bodies of irradiated mice have maintained and amplified superiorly to the co-culture with cells into which SCR-5 is not introduced, during the co-culture period. From the 5 results, it is revealed that an activity of stromal cells to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells is increased by high expression of SCR-5. Therefore, it is revealed that a gene product of SCR-5 10 has an activity to affect hematopoietic stem cells or hematopoietic progenitor cells to support survival or proliferation thereof or an activity to affect stromal cells to enhance a hematopoietic cell-supporting activity of the stromal cells or impart the activity to 15 the stromal cells.

Example 6 Cloning of SCR-6 and activity determination

Based on the nucleotide sequence of SEQ ID NO: 5, a probe was prepared and AGM-s3-A9 cDNA was screened by 20 hybridization to obtain a gene containing ORF of mouse SCR-6.

AGM-s3-A9 cells (1.4×10^8 cells) were dissolved in 20 mL of ISOGEN (Nippon gene, Japan) and total RNAs were prepared according to the attachment. Messenger RNAs 25 were prepared from one milligram of the total RNAs according to the protocol of the mRNA purification kit (Amersham Pharmacia, U.S.A.). By using SMART cDNA

library construction kit (CLONTECH, U.S.A.), cDNA libraries devided to 15 fractions were prepared from the 2 μ g of the prepared mRNAs according to the attachment. The libraries contained about 400,000 of independent 5 clones in total. For each fraction, PCR was performed under the following conditions to identify a fraction containing SCR-6 cDNA.

Based on the sequence of a partial fragment of the mouse SCR-6 gene, the following primers were prepared, 10 and PCR was performed with 35 cycles of 94°C, 30 seconds, 55°C, 30 seconds and 72°C, 1 minute, by using each fraction of AGM-s3-A9 cDNA libraries as a template.

SCR-6F

AGCTCATTACTGTATATTAA (SEQ ID NO: 22; 1971-1990)
15 (SEQ ID NO: 38)

SCR-6R

GCTATATTCATAAGTCATC (SEQ ID NO: 22; 2330-2349)
(SEQ ID NO: 39)

20 The PCR product was subjected to 2% agarose gel electrophoresis and a fraction from which the PCR product having the expected size was obtained was identified. For each of two fractions among the positive fractions, 50,000 plaques were seeded on two 25 15-cm petri dishes and incubated 37°C for 10 hours. Then, plaques of each petri dish were replicated to a sheet of Biodyne nylon filter (Pall, U.S.A.). The

replicated nylon filter was subjected to DNA fixation treatment according to the attachment, and screening with ³²P-labeled DNA probe was performed.

The probe was prepared as follows. PCR was

5 performed with 35 cycles of 94°C, 30 seconds, 55°C, 30 seconds and 72°C, 1 minute, by using SCR-6F and SCR-6R and the plasmid containing a partial fragment of the mouse SCR-6 gene as a template. The PCR product was subjected to 2% agarose gel electrophoresis and the 10 amplified fragment was purified by JETSORB. By using 25 ng of the obtained PCR fragment, ³²P-labeled DNA probe was prepared with Megaprime labeling kit (Amersham Pharmacia, U.S.A.).

Hybridization and washing were performed with

15 ExpressHybSolution (CLONETECH, U.S.A.) according to the attachment. An X-ray film was exposed to the filter and developed with a Fuji film auto developer to analyze the result. A plaque at a position corresponding to the resultant strongly exposed portion was scraped from the 20 petri dish, and seeded again so that about 200 of plaques should appear on 10-cm petri dish. Screening was again performed according to the above-mentioned method to isolate a single plaque. The obtained phage clone was transfected to *E. coli* strain BM25.8 according 25 to the attachment of SMART cDNA library construction kit, and allowed to be converted to plasmid in the cells to form colony on LB agar medium containing 50 µg/ml

ampicillin. A single colony of the transfected *E. coli* was inoculated to 3 ml of LB medium containing 50 µg/ml ampicillin and cultured at 30°C overnight. Plasmid was extracted with RPM kit (BIO101, U.S.A.) to obtain about 5 10 mg of plasmid.

Sequencing the both ends of the inserted fragment with an ABI377 DNA sequencer by using λTriplEx5'LD-Insert Screening Amplimer (CTCGGGAAAGCGCGCCATTGTGTTGGT (SEQ ID NO: 40); CLONTECH, U.S.A.) revealed that it 10 included cDNA containing the nucleotide sequence from nucleotide 1 of SEQ ID NO: 5. The full-length nucleotide sequence was also determined with the ABI377 DNA sequencer. The nucleotide sequence and the amino acid sequence deduced from a nucleotide sequence 15 predicted as ORF in the nucleotide sequence are shown in SEQ ID NO: 22. Only the amino acid sequence is shown in SEQ ID NO: 23.

By searching the cDNA database of KAZUSA DNA Institute for mouse SCR-6 nucleotide sequence with BLAST, 20 it has been found homologous *Homo sapiens* clone HJ08186R. HJ08186R has a high homology to the nucleotide sequence from guanine at nucleotide position 319 to adenine at nucleotide position 917 of mouse SCR-6, but is not predicted to have an entire ORF sequence.

25 KF305X primer; 5' - CCG CTC GAG CCG CCC AGA TGC AGT TTC GC -3' (SEQ ID NO: 49) having Xho I site at 5'-end was prepared according to the nucleotide sequence of

HJ08186R, 5'- CCG CCC AGA TGC AGT TTC GC -3' (nucleotide position: 10-29 in SEQ ID NO: 49), which is homologous to predicted initial methionine coding region of mouse SCR-6. 3'-RACE was performed with KOD-PLUS- (TOYOBO #KOD201) for the DNA polymerase and the enzyme reaction system by following protocol in the package insert. Primers used for amplification were KF305X primer for 5'-end primer and AP1 primer in Marathon Ready cDNA (CLONTECH) for 3'-end primer (0.2 μ M of each final concentration). Marathon Ready cDNA Human Fetal Liver (CLONTECH#7403-1) was used as a template. PCR was performed with GeneAmp PCR System 9700 (Applied Biosystems). Amplification was performed with 94°C for 5 minutes; 5 cycles of 94°C, 10 seconds, 72°C, 4 minutes; 5 cycles of 94°C, 10 seconds, 70°C, 4 minutes; 20 cycles of 94°C, 10 seconds, 68°C, 4 minutes; 72°C for 7 minutes and thereafter 4°C. By using 1/50 volume (1 μ l) of the amplified product, 2nd amplification was further performed with KF305X primer for 5'-end primer and AP2 primer for 3'-end primer (0.2 μ M of each final concentration). The 2nd amplification was performed with 94°C for 5 minutes; 5 cycles of 94°C, 10 seconds, 72°C, 4 minutes; 5 cycles of 94°C, 10 seconds, 70°C, 4 minutes; 35 cycles of 94°C, 10 seconds, 68°C, 4 minutes; 72°C for 7 minutes and thereafter 4°C. As a result, an amplified band of about 2 kilo base pairs was obtained.

The 2nd amplified product was incubated with dNTPs

(40 μ M of final concentration) and 5 units of Takara Taq (Takara Shuzo#R001A) at 72°C for 7 minutes and subjected to agarose gel electrophoresis. A DNA fragment about 2 kilo base pairs in size was identified and purified by 5 JETSORB Gel Extraction Kit (Genomed#110150). The purified DNA fragment was inserted to the pGEM-T Easy vector (Promega) by conventional method.

The nucleotide sequences of obtained clones were determined with the ABI377 DNA sequencer (Applied 10 Biosystems). The nucleotide sequence and amino acid sequence deduced from a nucleotide sequence predicted as ORF are shown in SEQ ID NO: 47. Only the amino acid sequence is shown in SEQ ID NO: 48. The nucleotide sequence contains a predicted ORF of 732 base pairs in 15 size (nucleotide position: 18-749 in SEQ ID NO: 47) and has homology with the mouse SCR-6 coding region at 92.3% (nucleotide sequence) and 95.9% (amino acid sequence). Thus, the sequence was identified as a counterpart of mouse SCR-6 in human and defined as human SCR-6. The 20 homology was determined with homology search in the compare function of DNASIS version 3.7 (Hitachi Software Engineering).

Determination of the activity of SCR-6 to support the hematopoietic stem cells or hematopoietic progenitor 25 cells was performed as follows.

(1) Construction of retrovirus vector for expression of mouse SCR-6

Based on the nucleotide sequence of SCR-6 ORF, SCR-6FxhoI and SCR-6Reco primers having the following sequences were prepared for retrovirus cloning, and PCR was performed by using DNA having the nucleotide 5 sequence shown in SEQ ID NO: 22 as a template. An amplified fragment was inserted to the retrovirus vector pMX-IRES-GFP in the same manner as described in (1) of Example 2.

SCR-6FxhoI

10 ccgctcgagccaccATGCGTTTTGCCTCTCTC (SEQ ID NO: 41)

SCR-6Reco

cggaattcTTATTGGTTCACTCTGTCTG (SEQ ID NO: 42)

(2) Preparation of stromal cells highly expressing SCR-6
15 AGM-s3-A9 cells in which SCR-6 was highly expressed
were prepared by using the above retrovirus vector in
the same manner as (2) of Example 2.

(3) Co-culture of human hematopoietic stem cells and
stromal cells highly expressing SCR-6, and determination
20 of proliferation statuses of hematopoietic stem cells
and hematopoietic progenitor cells by clonogenic assay

 In the same manner as described in (III) (1) 3) to
4) of Example 1, AGM-s3-A9 cells in which SCR-6 was
highly expressed through retrovirus, AGM-s3-A9 cells
25 into which a control vector was introduced, or AGM-s3-A9
cells were co-cultured with CD34-positive hematopoietic
stem cells derived from human cord blood, and

proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells are determined.

Fig. 9 shows results when the CD34-positive hematopoietic stem cells were co-cultured with AGM-S3-A9 cells in which SCR-6 was highly expressed (A9/SCR-9), AGM-S3-A9 cells into which a control vector was introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks. As a result, the co-culture with AGM-S3-A9 cells in which SCR-6 was highly expressed, increases of BFU-E and CFU-C were observed. Therefore, it has been revealed that the activity to support hematopoietic stem cells or hematopoietic progenitor cells, of AGM-S3-A9 increases by allowing SCR-6 to be highly expressed. From the results, it has been revealed that the gene product of SCR-6 has an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells or an activity to affect stromal cells to enhance a hematopoietic cell-supporting activity of the stromal cells or impart the activity to the stromal cells.

Example 7 Cloning of SCR-7 and activity determination

In the nucleotide sequence of SEQ ID NO: 6 obtained by the SBH analysis, the presence of ORF was predicted. The nuclotide sequence of ORF and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 24. Only the amino acid sequence is shown

in SEQ ID NO: 25.

Determination of the activity of SCR-7 to support the hematopoietic stem cells or hematopoietic progenitor cells was performed as follows.

5 (1) Construction of retrovirus vector for expression of mouse SCR-7

Based on the nucleotide sequence of SCR-7 ORF, SCR-7FsalI and SCR-7Reco primers having the following nucleotide sequences were prepared for retrovirus 10 cloning, and PCR was performed using DNA having the nucleotide sequence shown in SEQ ID NO: 24 as a template.

An amplified fragment was inserted to the retrovirus vector pMX-IRES-GFP in the same manner as described in (1) of Example 2.

15 SCR-7FsalI

acgcgtcgaccaccATGCCCGCTACGAGTTG (SEQ ID NO: 43)

SCR-7Reco

attGAATTCTCACTTCTTCCTCCTCTTG (SEQ ID NO: 44)

20 (2) Preparation of stromal cells highly expressing SCR-7 AGM-s3-A9 cells in which SCR-7 was highly expressed were prepared by using the above retrovirus vector in the same manner as (2) of Example 2.

(3) Co-culture of human hematopoietic stem cells and 25 stromal cells highly expressing SCR-7, and determination of proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells by clonogenic assay

In the same manner as described in (III) (1) 3) to 4) of Example 1, AGM-s3-A9 cells in which SCR-7 was highly expressed through retrovirus, AGM-s3-A9 cells into which a control vector was introduced, or AGM-s3-A9 5 cells were co-cultured with CD34-positive hematopoietic stem cells derived from human cord blood, and proliferation statuses of hematopoietic stem cells and hematopoietic progenitor cells are determined.

Fig. 10 shows results when the CD34-positive 10 hematopoietic stem cells were co-cultured with AGM-S3-A9 cells in which SCR-7 was highly expressed (A9/SCR-7), AGM-S3-A9 cells into which a control vector was introduced (A9/pMXIG) or AGM-S3-A9 cells (A9) for two weeks. As a result, the co-culture with AGM-S3-A9 cells 15 in which SCR-7 was highly expressed, increases of BFU-E and CFU-C were observed. Therefore, it has been revealed that the activity to support hematopoietic stem cells or hematopoietic progenitor cells, of AGM-S3-A9 increases by allowing SCR-7 to be highly expressed. 20 From the results, it has been revealed that the gene product of SCR-7 has an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor cells or an activity to affect stromal cells to enhance a hematopoietic cell-supporting 25 activity of the stromal cells or impart the activity to the stromal cells.

Example 8 Cloning of SCR-8 and activity determination

By searching GenBank database for the nucleotide sequence shown in SEQ ID NO: 7 with BLAST, it has been found that SCR-8 is the same gene as *Mus musculus* mRNA for ADAM23 of an accession number AB009673. The nucleotide sequence of SCR-8 ORF and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 26. Only the amino acid sequence is shown in SEQ ID NO: 27.

10 Also, the sequence encoding Human MDC3 protein [*Homo sapiens*] described by JP 11155574-A has a homology of not less than 90% with SCR-8 and, therefore, is a human ortholog of SCR-8. The nucleotide sequence of this ORF and the amino acid sequence deduced from the nucleotide sequence are shown in SEQ ID NO: 28. Only the amino acid sequence is shown in SEQ ID NO: 29.

Determination of the activity of SCR-8 to support the hematopoietic stem cells or hematopoietic progenitor cells was performed as follows.

20 (1) Construction of retrovirus vector for expression of mouse SCR-8

Based on the nucleotide sequence of SCR-8 ORF, SCR-8F_{Xba}I and SCR-8R_{co} primers having the following nucleotide sequences were prepared, and PCR was performed using AGM-s3-A9 cDNA as a template. An amplified fragment was inserted to the retrovirus vector pMX-IRES-GFP in the same manner as described in (1) of

Example 2.

SCR-8F_xhoI

ccgctcgagccaccATGAAGCCGCCGGCAGCATIC (SEQ ID NO: 45)

SCR-8Reco

5 cggaattcTCAGATGGGGCCTTGCTGAGT (SEQ ID NO: 46)

(2) Preparation of stromal cells highly expressing SCR-8

AGM-s3-A9 cells in which SCR-8 was highly expressed
were prepared by using the above retrovirus vector in

10 the same manner as (2) of Example 2.

(3) Co-culture of human hematopoietic stem cells and
stromal cells highly expressing SCR-8, and determination
of proliferation statuses of hematopoietic stem cells
and hematopoietic progenitor cells by clonogenic assay

15 In the same manner as described in (III) (1) 3) to

4) of Example 1, AGM-s3-A9 cells in which SCR-8 was

highly expressed through retrovirus, AGM-s3-A9 cells
into which a control vector was introduced, or AGM-s3-A9
cells were co-cultured with CD34-positive hematopoietic

20 stem cells derived from human cord blood, and

proliferation statuses of hematopoietic stem cells and
hematopoietic progenitor cells are determined.Fig. 11 shows results when the CD34-positive
hematopoietic stem cells were co-cultured with AGM-S3-A9
25 cells in which SCR-8 was highly expressed, AGM-S3-A9
cells into which a control vector was introduced or
AGM-S3-A9 cells for two weeks. As a result, the co-

culture with AGM-S3-A9 cells in which SCR-8 was highly expressed, increases of BFU-E and CFU-C were observed. Therefore, it has been revealed that the activity to support hematopoietic stem cells or hematopoietic 5 progenitor cells, of AGM-S3-A9 increases by allowing SCR-8 to be highly expressed. From the results, it has been revealed that the gene product of SCR-8 has an activity to support survival or proliferation of hematopoietic stem cells or hematopoietic progenitor 10 cells or an activity to affect stromal cells to enhance a hematopoietic cell-supporting activity of the stromal cells or impart the activity to the stromal cells.

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Asn Val Leu Lys Gly Cys Leu Ala Asn Gln Ala Asp Leu Asp Ala Glu
 275 280 285

Trp Arg Asn Leu Leu Asp Ser Met Val Leu Ile Thr Asp Lys Phe Trp
 290 295 300

Gly Pro Ser Gly Ala Glu Ser Val Ile Gly Gly Val His Val Trp Leu
 305 310 315 320

Ala Glu Ala Ile Asn Ala Leu Gln Asp Asn Lys Asp Thr Leu Thr Ala
 325 330 335

Lys Val Ile Gln Ala Cys Gly Asn Pro Lys Val Asn Pro His Gly Ser
 340 345 350

Gly Pro Glu Glu Lys Arg Arg Gly Lys Leu Ala Leu Gln Glu Lys
 355 360 365

Pro Ser Thr Gly Thr Leu Glu Lys Leu Val Ser Glu Ala Lys Ala Gln
 370 375 380

Leu Arg Asp Ile Gln Asp Phe Trp Ile Ser Leu Pro Gly Thr Leu Cys
 385 390 395 400

Ser Glu Lys Met Ala Met Ser Pro Ala Ser Asp Asp Arg Cys Trp Asn
 405 410 415

Gly Ile Ser Lys Gly Arg Tyr Leu Pro Glu Val Met Gly Asp Gly Leu
 420 425 430

Ala Asn Gln Ile Asn Asn Pro Glu Val Glu Val Asp Ile Thr Lys Pro
 435 440 445

Asp Met Thr Ile Arg Gln Gln Ile Met Gln Leu Lys Ile Met Thr Asn
 450 455 460

Arg Leu Arg Gly Ala Tyr Gly Gly Asn Asp Val Asp Phe Gln Asp Ala
 465 470 475 480

Ser Asp Asp Gly Ser Gly Ser Gly Ser Gly Gly Cys Pro Asp Asp
 485 490 495

Thr Cys Gly Arg Arg Val Ser Lys Lys Ser Ser Ser Arg Thr Pro
 500 505 510

Leu Thr His Ala Leu Pro Gly Leu Ser Glu Gln Glu Gly Gln Lys Thr
 515 520 525

Ser Ala Ala Thr Cys Pro Glu Pro His Ser Phe Phe Leu Leu Phe Leu
 530 535 540

Val Thr Leu Val Leu Ala Ala Ala Arg Pro Arg Trp Arg
 545 550 555

<210> 10
 <211> 1677
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(1674)

<400> 10
 atg gag ctc cgg gcc cga ggc tgg tgg ctg cta tgt gcg gcc gca gcg 48
 Met Glu Leu Arg Ala Arg Gly Trp Trp Leu Leu Cys Ala Ala Ala
 1 5 10 15

ctg gtc gcc tgc gcc cgc ggg gac ccg gcc agc aag agc ccg agc tgc 96
 Leu Val Ala Cys Ala Arg Gly Asp Pro Ala Ser Lys Ser Arg Ser Cys
 20 25 30

ggc gag gtc cgc cag atc tac gga gcc aag ggc ttc agc ctg agc gac 144
 Gly Glu Val Arg Gln Ile Tyr Gly Ala Lys Gly Phe Ser Leu Ser Asp
 35 40 45

gtg ccc cag gcg gag atc tcc ggt gag cac ctg cgg atc tgt ccc cag 192
 Val Pro Gln Ala Glu Ile Ser Gly Glu His Leu Arg Ile Cys Pro Gln
 50 55 60

ggc tac acc tgc acc agc gag atg gag gag aac ctg gcc aac cgc 240
 Gly Tyr Thr Cys Cys Thr Ser Glu Met Glu Glu Asn Leu Ala Asn Arg
 65 70 75 80

agc cat gcc gag ctg gag acc gcg ctc cgg gac agc agc cgc gtc ctg 288
 Ser His Ala Glu Leu Glu Thr Ala Leu Arg Asp Ser Ser Arg Val Leu
 85 90 95

cag gcc atg ctt gcc acc cag ctg cgc agc ttc gat gac cac ttc cag 336

Gln Ala Met Leu Ala Thr Gln Leu Arg Ser Phe Asp Asp His Phe Gln	100	105	110	
cac ctg ctg aac gac tac gag gag cgg acg ctg cag gcc acc ttc ccc ggc				384
His Leu Leu Asn Asp Ser Glu Arg Thr Leu Gln Ala Thr Phe Pro Gly				
115 120 125				
gcc ttc gga gag ctg tac acg cag aac gcg agg gcc ttc cgg gac ctg				432
Ala Phe Gly Glu Leu Tyr Thr Gln Asn Ala Arg Ala Phe Arg Asp Leu				
130 135 140				
tac tca gag ctg cgc ctg tac tac cgc ggt gcc aac ctg cac ctg gag				480
Tyr Ser Glu Leu Arg Leu Tyr Tyr Arg Gly Ala Asn Leu His Leu Glu				
145 150 155 160				
gag acg ctg gcc gag ttc tgg gcc cgc ctg ctc gag cgc ctc ttc aag				528
Glu Thr Leu Ala Glu Phe Trp Ala Arg Leu Leu Glu Arg Leu Phe Lys				
165 170 175				
cag ctg cac ccc cag ctg ctg ctc gat gac tac ctg gac tgc ctg				576
Gln Leu His Pro Gln Leu Leu Pro Asp Asp Tyr Leu Asp Cys Leu				
180 185 190				
ggc aag gag gcc gag ggc ctg cgg ccc ttc ggg gag gcc ccc aga gag				624
Gly Lys Gln Ala Glu Ala Leu Arg Pro Phe Gly Glu Ala Pro Arg Glu				
195 200 205				
ctg cgc ctg cgg gcc acc cgt gcc ttc gtg gct gct cgc tcc ttt gtg				672
Leu Arg Leu Arg Ala Thr Arg Ala Phe Val Ala Ala Arg Ser Phe Val				
210 215 220				
cag ggc ctg ggc gtg gcc agc gac gtg gtc cgg aaa gtg gct cag gtc				720
Gln Gly Leu Gly Val Ala Ser Asp Val Val Arg Lys Val Ala Gln Val				
225 230 235 240				
ccc ctg ggc ccc gag tgc tcg aga gct gtc atg aag ctg gtc tac tgt				768
Pro Leu Gly Pro Glu Cys Ser Arg Ala Val Met Lys Leu Val Tyr Cys				
245 250 255				
gct cac tgc ctg gga gtc ccc ggc goc agg ccc tgc cct gac tat tgc				816
Ala His Cys Leu Gly Val Pro Gly Ala Arg Pro Cys Pro Asp Tyr Cys				
260 265 270				
cga aat gtg ctc aag ggc tgc ctt gcc aac cag gcc gac ctg gac gcc				864
Arg Asn Val Leu Lys Gly Cys Leu Ala Asn Gln Ala Asp Leu Asp Ala				
275 280 285				
gag tgg agg aac ctc ctg gac tcc atg gtg ctc atc acc gac aag ttc				912
Glu Trp Arg Asn Leu Leu Asp Ser Met Val Leu Ile Thr Asp Lys Phe				
290 295 300				
tgg ggt aca tcg ggt gtg gag agt gtc atc ggc agc gtg cac acg tgg				960
Trp Gly Thr Ser Gly Val Glu Ser Val Ile Gly Ser Val His Thr Trp				
305 310 315 320				
ctg gcc gag gcc atc aac gcc ctc cag gac aac agg gac acg ctc acg				1008

Leu Ala Glu Ala Ile Asn Ala Leu Gln Asp Asn Arg Asp Thr Leu Thr			
325	330	335	
gcc aag gtc atc cag ggc tgc ggg aac ccc aag gtc aac ccc cag ggc			1056
Ala Lys Val Ile Gln Gly Cys Gly Asn Pro Lys Val Asn Pro Gln Gly			
340	345	350	
cct ggg cct gag gag aag cgg cgc cgg ggc aag ctg gcc ccc cgg gag			1104
Pro Gly Pro Glu Glu Lys Arg Arg Gly Lys Leu Ala Pro Arg Glu			
355	360	365	
agg cca cct tca ggc acg ctg gag aag ctg gtc tct gaa gcc aag gcc			1152
Arg Pro Pro Ser Gly Thr Leu Glu Lys Leu Val Ser Glu Ala Lys Ala			
370	375	380	
cag ctc cgc gac gtc cag gac ttc tgg atc agc ctc cca ggg aca ctg			1200
Gln Leu Arg Asp Val Gln Asp Phe Trp Ile Ser Leu Pro Gly Thr Leu			
385	390	395	400
tgc agt gag aag atg gcc ctg agc act gcc agt gat gac cgc tgc tgg			1248
Cys Ser Glu Lys Met Ala Leu Ser Thr Ala Ser Asp Asp Arg Cys Trp			
405	410	415	
aac ggg atg gcc aga ggc cgg tac ctc ccc gag gtc atg ggt gac ggc			1296
Asn Gly Met Ala Arg Gly Arg Tyr Leu Pro Glu Val Met Gly Asp Gly			
420	425	430	
ctg gcc aac cag atc aac aac ccc gag gtg gag gtg gac atc acc aag			1344
Leu Ala Asn Gln Ile Asn Asn Pro Glu Val Glu Val Asp Ile Thr Lys			
435	440	445	
ccg gac atg acc atc cgg cag cag atc atg cag ctg aag atc atg acc			1392
Pro Asp Met Thr Ile Arg Gln Gln Ile Met Gln Leu Lys Ile Met Thr			
450	455	460	
aac cgg ctg cgc agc gcc tac aac ggc aac gac gtg gac ttc cag gac			1440
Asn Arg Leu Arg Ser Ala Tyr Asn Gly Asn Asp Val Asp Phe Gln Asp			
465	470	475	480
gcc agt gac gac ggc agc ggc tgc ggc agc ggt gat ggc tgt ctg gat			1488
Ala Ser Asp Asp Gly Ser Gly Ser Gly Asp Gly Cys Leu Asp			
485	490	495	
gac ctc tgc ggc cgg aag gtc agc agg aag agc tcc agc tcc cgg agc			1536
Asp Leu Cys Gly Arg Lys Val Ser Arg Lys Ser Ser Ser Arg Thr			
500	505	510	
ccc ttg acc cat gcc ctc cca ggc ctg tca gag cag gaa gga cag aag			1584
Pro Leu Thr His Ala Leu Pro Glu Leu Ser Glu Gln Glu Gly Gln Lys			
515	520	525	
acc tcg gct gcc agc tgc ccc cag ccc ccc acc ttc ctc ctg ccc ctc			1632
Thr Ser Ala Ala Ser Cys Pro Gln Pro Pro Thr Phe Leu Leu Pro Leu			
530	535	540	
ctc ctc ttc ctg gcc ctt aca gta gcc agg ccc cgg tgg cgg taa			1677

Leu Leu Phe Leu Ala Leu Thr Val Ala Arg Pro Arg Trp Arg
 545 550 555

<210> 11
 <211> 558
 <212> PRT
 <213> Homo sapiens

<400> 11
 Met Glu Leu Arg Ala Arg Gly Trp Trp Leu Leu Cys Ala Ala Ala Ala
 1 5 10 15

Leu Val Ala Cys Ala Arg Gly Asp Pro Ala Ser Lys Ser Arg Ser Cys
 20 25 30

Gly Glu Val Arg Gln Ile Tyr Gly Ala Lys Gly Phe Ser Leu Ser Asp
 35 40 45

Val Pro Gln Ala Glu Ile Ser Gly Glu His Leu Arg Ile Cys Pro Gln
 50 55 60

Gly Tyr Thr Cys Cys Thr Ser Glu Met Glu Glu Asn Leu Ala Asn Arg
 65 70 75 80

Ser His Ala Glu Leu Glu Thr Ala Leu Arg Asp Ser Ser Arg Val Leu
 85 90 95

Gln Ala Met Leu Ala Thr Gln Leu Arg Ser Phe Asp Asp His Phe Gln
 100 105 110

His Leu Leu Asn Asp Ser Glu Arg Thr Leu Gln Ala Thr Phe Pro Gly
 115 120 125

Ala Phe Gly Glu Leu Tyr Thr Gln Asn Ala Arg Ala Phe Arg Asp Leu
 130 135 140

Tyr Ser Glu Leu Arg Leu Tyr Tyr Arg Gly Ala Asn Leu His Leu Glu
 145 150 155 160

Glu Thr Leu Ala Glu Phe Trp Ala Arg Leu Leu Glu Arg Leu Phe Lys
 165 170 175

Gln Leu His Pro Gln Leu Leu Pro Asp Asp Tyr Leu Asp Cys Leu
 180 185 190

Gly Lys Gln Ala Glu Ala Leu Arg Pro Phe Gly Glu Ala Pro Arg Glu
 195 200 205

Leu Arg Leu Arg Ala Thr Arg Ala Phe Val Ala Ala Arg Ser Phe Val
 210 215 220

Gln Gly Leu Gly Val Ala Ser Asp Val Val Arg Lys Val Ala Gln Val
 225 230 235 240

Pro Leu Gly Pro Glu Cys Ser Arg Ala Val Met Lys Leu Val Tyr Cys
 245 250 255

Ala His Cys Leu Gly Val Pro Gly Ala Arg Pro Cys Pro Asp Tyr Cys
 260 265 270

Arg Asn Val Leu Lys Gly Cys Leu Ala Asn Gln Ala Asp Leu Asp Ala
 275 280 285

Glu Trp Arg Asn Leu Leu Asp Ser Met Val Leu Ile Thr Asp Lys Phe
 290 295 300

Trp Gly Thr Ser Gly Val Glu Ser Val Ile Gly Ser Val His Thr Trp
 305 310 315 320

Leu Ala Glu Ala Ile Asn Ala Leu Gln Asp Asn Arg Asp Thr Leu Thr
 325 330 335

Ala Lys Val Ile Gln Gly Cys Gly Asn Pro Lys Val Asn Pro Gln Gly
 340 345 350

Pro Gly Pro Glu Glu Lys Arg Arg Arg Gly Lys Leu Ala Pro Arg Glu
 355 360 365

Arg Pro Pro Ser Gly Thr Leu Glu Lys Leu Val Ser Glu Ala Lys Ala
 370 375 380

Gln Leu Arg Asp Val Gln Asp Phe Trp Ile Ser Leu Pro Gly Thr Leu
 385 390 395 400

Cys Ser Glu Lys Met Ala Leu Ser Thr Ala Ser Asp Asp Arg Cys Trp
 405 410 415

Asn Gly Met Ala Arg Gly Arg Tyr Leu Pro Glu Val Met Gly Asp Gly
 420 425 430

Leu Ala Asn Gln Ile Asn Asn Pro Glu Val Glu Val Asp Ile Thr Lys
 435 440 445

Pro Asp Met Thr Ile Arg Gln Gln Ile Met Gln Leu Lys Ile Met Thr
 450 455 460

Asn Arg Leu Arg Ser Ala Tyr Asn Gly Asn Asp Val Asp Phe Gln Asp
 465 470 475 480

Ala Ser Asp Asp Gly Ser Gly Ser Gly Asp Gly Cys Leu Asp
 485 490 495

Asp Leu Cys Gly Arg Lys Val Ser Arg Lys Ser Ser Ser Arg Thr
 500 505 510

Pro Leu Thr His Ala Leu Pro Gly Leu Ser Glu Gln Glu Gly Gln Lys
 515 520 525

Thr Ser Ala Ala Ser Cys Pro Gln Pro Pro Thr Phe Leu Leu Pro Leu
 530 535 540

Leu Leu Phe Leu Ala Leu Thr Val Ala Arg Pro Arg Trp Arg
 545 550 555

<210> 12
 <211> 369
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)..(366)

<400> 12
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 Met Lys Pro Phe His Thr Ala Leu Ser Phe Leu Ile Leu Thr Thr Ala
 1 5 10 15 48

ctt gga atc tgg gcc cag atc aca cat gca aca gag aca aaa gaa gtc
 Leu Gly Ile Trp Ala Gln Ile Thr His Ala Thr Glu Thr Lys Glu Val
 20 25 30 96

cag	agc	agt	ctg	aag	gca	cag	caa	ggg	ctt	gaa	att	gaa	atg	ttt	cac	144
Gln	Ser	Ser	Leu	Lys	Ala	Gln	Gln	Gly	Leu	Glu	Ile	Glu	Met	Phe	His	
35						35			40			45				
atg	ggc	ttt	caa	gac	tct	tca	gat	tgc	tgc	ctg	tcc	tat	aac	tca	cgg	192
Met	Gly	Phe	Gln	Asp	Ser	Ser	Asp	Cys	Cys	Leu	Ser	Tyr	Asn	Ser	Arg	
50						50			55			60				
att	cag	tgt	tca	aga	ttt	ata	ggt	tat	ttt	ccc	acc	agt	ggt	ggg	tgt	240
Ile	Gln	Cys	Ser	Arg	Phe	Ile	Gly	Tyr	Phe	Pro	Thr	Ser	Gly	Gly	Cys	
65						70			75			80				
acc	agg	cgg	ggc	atc	atc	ttt	atc	agc	aag	agg	ggg	ttc	cag	gtc	tgt	288
Thr	Arg	Pro	Gly	Ile	Ile	Phe	Ile	Ser	Lys	Arg	Gly	Phe	Gln	Val	Cys	
								85			90			95		
gcc	aac	ccc	agt	gat	cgg	aga	gtt	cag	aga	tgc	att	gaa	aga	ttg	gag	336
Ala	Asn	Pro	Ser	Asp	Arg	Arg	Val	Gln	Arg	Cys	Ile	Glu	Arg	Leu	Glu	
							100			105			110			
caa	aac	tca	caa	cca	cgg	acc	tac	aaa	caa	taa						369
Gln	Asn	Ser	Gln	Pro	Arg	Thr	Tyr	Lys	Gln							
						115			120							
<210>	13															
<211>	122															
<212>	PRT															
<213>	Mus	musculus														
<400>	13															
Met	Lys	Pro	Phe	His	Thr	Ala	Leu	Ser	Phe	Leu	Ile	Leu	Thr	Thr	Ala	
1							5			10			15			
Leu	Gly	Ile	Trp	Ala	Gln	Ile	Thr	His	Ala	Thr	Glu	Thr	Lys	Glu	Val	
							20			25			30			
Gln	Ser	Ser	Leu	Lys	Ala	Gln	Gln	Gly	Leu	Glu	Ile	Glu	Met	Phe	His	
						35			40			45				
Met	Gly	Phe	Gln	Asp	Ser	Ser	Asp	Cys	Cys	Leu	Ser	Tyr	Asn	Ser	Arg	
							50			55			60			
Ile	Gln	Cys	Ser	Arg	Phe	Ile	Gly	Tyr	Phe	Pro	Thr	Ser	Gly	Gly	Cys	
65							70			75			80			
Thr	Arg	Pro	Gly	Ile	Ile	Phe	Ile	Ser	Lys	Arg	Gly	Phe	Gln	Val	Cys	
								85			90			95		
Ala	Asn	Pro	Ser	Asp	Arg	Arg	Val	Gln	Arg	Cys	Ile	Glu	Arg	Leu	Glu	

100

100

105

110

Gln Asn Ser Gln Pro Arg Thr Tyr Lys Gln
 115 120

<210> 14
 <211> 1223
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (84)..(1121)

<400> 14
 gtgaccggaa agggagcccc gtggtagagg tgacggagc tgacgatttc agatctgctt 60
 agtaaacccg tgtatcgccc acc atg ttg gct gca agg ctt gtg tgt ctc cgg 113
 Met Leu Ala Ala Arg Leu Val Cys Leu Arg
 1 5 10
 aca cta cct tcc agg gtt ttc cag ccc act ttc atc acc aag gcc tct 161
 Thr Leu Pro Ser Arg Val Phe Gln Pro Thr Phe Ile Thr Lys Ala Ser
 15 20 25
 cca ctt gtg aag aat tcc atc aca aag aac caa tgg ctc gta aca ccc 209
 Pro Leu Val Lys Asn Ser Ile Thr Lys Asn Gln Trp Leu Val Thr Pro
 30 35 40
 agc agg gaa tat gct acc aag aca aga att agg act cac cgt ggg aaa 257
 Ser Arg Glu Tyr Ala Thr Lys Thr Arg Ile Arg Thr His Arg Gly Lys
 45 50 55
 act gga caa gaa ctg aaa gag gca gcc ttg gaa cca tca atg gaa aaa 305
 Thr Gly Gln Glu Leu Lys Glu Ala Ala Leu Glu Pro Ser Met Glu Lys
 60 65 70
 atc ttt aaa atc gat caa atg gga agg tgg ttt gtt gct gga gga gca 353
 Ile Phe Lys Ile Asp Gln Met Gly Arg Trp Phe Val Ala Gly Gly Ala
 75 80 85 90
 gct gtt ggt ctt gga gcg ctc tgc tac tat ggc ttg gga atg tct aat 401
 Ala Val Gly Leu Gly Ala Leu Cys Tyr Tyr Gly Leu Gly Met Ser Asn
 95 100 105
 gag att gga gct atc gaa aag gct gta att tgg cct cag tat gta aag 449
 Glu Ile Gly Ala Ile Glu Lys Ala Val Ile Trp Pro Gln Tyr Val Lys
 110 115 120
 gat aga att cat tct act tac atg tac tta gca gga agg tat tgt tta 497
 Asp Arg Ile His Ser Thr Tyr Met Tyr Leu Ala Gly Arg Tyr Cys Leu
 125 130 135
 aca gct ttg tct gcc ttg gca gta gcc aga aca cct gct ctc atg aac 545

Thr Ala Leu Ser Ala Leu Ala Val Ala Arg Thr Pro Ala Leu Met Asn			
140	145	150	
ttc atg atg aca ggc tct tgg gtg aca att ggt gcg acc ttt gca gcc			593
Phe Met Met Thr Gly Ser Trp Val Thr Ile Gly Ala Thr Phe Ala Ala			
155	160	165	170
atg att gga gct gga atg ctt gta cac tca ata tca tat gag cag agc			641
Met Ile Gly Ala Gly Met Leu Val His Ser Ile Ser Tyr Glu Gln Ser			
175	180	185	
cca ggc cca aag cat ctg gct tgg atg ctg cat tct ggt gtg atg ggt			689
Pro Gly Pro Lys His Leu Ala Trp Met Leu His Ser Gly Val Met Gly			
190	195	200	
gca gtt gtg gct cct ctg acg atc tta ggg ggg oct ctt ctc ctg aga			737
Ala Val Val Ala Pro Leu Thr Ile Leu Gly Gly Pro Leu Leu Leu Arg			
205	210	215	
gcc gca tgg tac acc gct ggt att gtg gga ggc ctc tct act gtg gcc			785
Ala Ala Trp Tyr Thr Ala Gly Ile Val Gly Gly Leu Ser Thr Val Ala			
220	225	230	
atg tgt gcg cct agt gag aag ttt ctg aac atg gga gca ccc ctg gga			833
Met Cys Ala Pro Ser Glu Lys Phe Leu Asn Met Gly Ala Pro Leu Gly			
235	240	245	250
gtg ggc ctg ggt ctt gtc ttt gcg tct tct ctg ggg tct atg ttt ctt			881
Val Gly Leu Gly Leu Val Phe Ala Ser Ser Leu Gly Ser Met Phe Leu			
255	260	265	
ccc oct acc tct gtg gct ggt gcc act ctg tac tca gtg gca atg tat			929
Pro Pro Thr Ser Val Ala Gly Ala Thr Leu Tyr Ser Val Ala Met Tyr			
270	275	280	
ggt gga tta gtt ctt ttc agc atg ttc ctt ctg tat gat act cag aaa			977
Gly Gly Leu Val Leu Phe Ser Met Phe Leu Leu Tyr Asp Thr Gln Lys			
285	290	295	
gta atc aaa cgt gca gaa ata aca ccc atg tat gga gct caa aag tat			1025
Val Ile Lys Arg Ala Glu Ile Thr Pro Met Tyr Gly Ala Gln Lys Tyr			
300	305	310	
gat ccc atc aat tcg atg ttg aca atc tac atg gat aca tta aat ata			1073
Asp Pro Ile Asn Ser Met Leu Thr Ile Tyr Met Asp Thr Leu Asn Ile			
315	320	325	330
ttt atg cga gtt gca act atg cta gca act gga agc aac aga aag aaa			1121
Phe Met Arg Val Ala Thr Met Leu Ala Thr Gly Ser Asn Arg Lys Lys			
335	340	345	
tgaagtaacc gcttgtatg tctccgtca ctgtatgttctt gcttgtttaa taggaggaga			1181
tagtcattac agtttgcatc agcagaattc ccgcgcggcc gc			1223

<210> 15
 <211> 346
 <212> PRT
 <213> *Mus musculus*

<400> 15
 Met Leu Ala Ala Arg Leu Val Cys Leu Arg Thr Leu Pro Ser Arg Val
 1 5 10 15

Phe Gln Pro Thr Phe Ile Thr Lys Ala Ser Pro Leu Val Lys Asn Ser
 20 25 30

Ile Thr Lys Asn Gln Trp Leu Val Thr Pro Ser Arg Glu Tyr Ala Thr
 35 40 45

Lys Thr Arg Ile Arg Thr His Arg Gly Lys Thr Gly Gln Glu Leu Lys
 50 55 60

Glu Ala Ala Leu Glu Pro Ser Met Glu Lys Ile Phe Lys Ile Asp Gln
 65 70 75 80

Met Gly Arg Trp Phe Val Ala Gly Gly Ala Ala Val Gly Leu Gly Ala
 85 90 95

Leu Cys Tyr Tyr Gly Leu Gly Met Ser Asn Glu Ile Gly Ala Ile Glu
 100 105 110

Lys Ala Val Ile Trp Pro Gln Tyr Val Lys Asp Arg Ile His Ser Thr
 115 120 125

Tyr Met Tyr Leu Ala Gly Arg Tyr Cys Leu Thr Ala Leu Ser Ala Leu
 130 135 140

Ala Val Ala Arg Thr Pro Ala Leu Met Asn Phe Met Met Thr Gly Ser
 145 150 155 160

Trp Val Thr Ile Gly Ala Thr Phe Ala Ala Met Ile Gly Ala Gly Met
 165 170 175

Leu Val His Ser Ile Ser Tyr Glu Gln Ser Pro Gly Pro Lys His Leu
 180 185 190

Ala Trp Met Leu His Ser Gly Val Met Gly Ala Val Val Ala Pro Leu
 195 200 205

Thr Ile Leu Gly Gly Pro Leu Leu Leu Arg Ala Ala Trp Tyr Thr Ala
 210 215 220

Gly Ile Val Gly Gly Leu Ser Thr Val Ala Met Cys Ala Pro Ser Glu
 225 230 235 240

Lys Phe Leu Asn Met Gly Ala Pro Leu Gly Val Gly Leu Gly Leu Val
 245 250 255

Phe Ala Ser Ser Leu Gly Ser Met Phe Leu Pro Pro Thr Ser Val Ala
 260 265 270

Gly Ala Thr Leu Tyr Ser Val Ala Met Tyr Gly Gly Leu Val Leu Phe
 275 280 285

Ser Met Phe Leu Leu Tyr Asp Thr Gln Lys Val Ile Lys Arg Ala Glu
 290 295 300

Ile Thr Pro Met Tyr Gly Ala Gln Lys Tyr Asp Pro Ile Asn Ser Met
 305 310 315 320

Leu Thr Ile Tyr Met Asp Thr Leu Asn Ile Phe Met Arg Val Ala Thr
 325 330 335

Met Leu Ala Thr Gly Ser Asn Arg Lys Lys
 340 345

<210> 16
 <211> 1038
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(1035)

<400> 16
 atg ttg gct gca agg ctg gtg tgt ctc cgg aca cta cct tct agg gtt 48
 Met Leu Ala Ala Arg Leu Val Cys Leu Arg Thr Leu Pro Ser Arg Val
 1 5 10 15

ttc cac cca gct ttc acc aag gcc tcc cct gtt gtg aag aat tcc atc 96
 Phe His Pro Ala Phe Thr Lys Ala Ser Pro Val Val Lys Asn Ser Ile
 20 25 30

acg aag aat caa tgg ctg tta aca cct agc agg gaa tat gcc acc aaa Thr Lys Asn Gln Trp Leu Leu Thr Pro Ser Arg Glu Tyr Ala Thr Lys 35 40 45	144
aca aga att ggg atc cgg cgt ggg aga act ggc caa gaa ctc aaa gag Thr Arg Ile Gly Ile Arg Arg Gly Arg Thr Gly Gln Glu Leu Lys Glu 50 55 60	192
gca gca ttg gaa cca tcg atg gaa aaa ata ttt aaa att gat cag atg Ala Ala Leu Glu Pro Ser Met Glu Lys Ile Phe Lys Ile Asp Gln Met 65 70 75 80	240
gga aga tgg ttt gtt gct gga ggg gct gct gtt ggt ctt gga gca ttg Gly Arg Trp Phe Val Ala Gly Ala Ala Val Gly Leu Gly Ala Leu 85 90 95	288
tgc tac tat ggc ttg gga ctg tct aat gag att gga gct att gaa aag Cys Tyr Tyr Gly Leu Ser Asn Glu Ile Gly Ala Ile Glu Lys 100 105 110	336
gct gta att tgg cct cag tat gtc aag gat aga att cat tcc acc tat Ala Val Ile Trp Pro Gln Tyr Val Lys Asp Arg Ile His Ser Thr Tyr 115 120 125	384
atg tac tta gca ggg agt att ggt tta aca gct ttg tct goc ata gca Met Tyr Leu Ala Gly Ser Ile Gly Leu Thr Ala Leu Ser Ala Ile Ala 130 135 140	432
atc agc aga acg cct gtt ctc atg aac ttc atg atg aga ggc tct tgg Ile Ser Arg Thr Pro Val Leu Met Asn Phe Met Met Arg Gly Ser Trp 145 150 155 160	480
gtg aca att ggt gtg acc ttt gca gcc atg gtt gga gct gga atg ctg Val Thr Ile Gly Val Thr Phe Ala Ala Met Val Gly Ala Gly Met Leu 165 170 175	528
gta cga tca ata cca tat gac cag agc cca ggc cca aag cat ctt gct Val Arg Ser Ile Pro Tyr Asp Gln Ser Pro Gly Pro Lys His Leu Ala 180 185 190	576
tgg ttg cta cat tct ggt gtg atg ggt gca gtg gtg gct cct ctg aca Trp Leu His Ser Gly Val Met Gly Ala Val Val Ala Pro Leu Thr 195 200 205	624
ata tta ggg ggt oct ctt ctc atc aga gct gca tgg tac aca gct ggc Ile Leu Gly Gly Pro Leu Leu Ile Arg Ala Ala Trp Tyr Thr Ala Gly 210 215 220	672
att gtg gga ggc ctc tcc act gtg gcc atg tgt ggc ccc agt gaa aag Ile Val Gly Gly Leu Ser Thr Val Ala Met Cys Ala Pro Ser Glu Lys 225 230 235 240	720
ttt ctg aac atg ggt gca ccc ctg gga gtg ggc ctg ggt ctc gtc ttt Phe Leu Asn Met Gly Ala Pro Leu Gly Val Gly Leu Gly Leu Val Phe 245 250 255	768

gtg tcc tca ttg gga tct atg ttt ctt cca cct acc acc gtg gct ggt
 Val Ser Ser Leu Gly Ser Met Phe Leu Pro Pro Thr Thr Val Ala Gly
 260 265 270

goc act ctt tac tca gtg gca atg tac ggt gga tta gtt ctt ttc agc
 Ala Thr Leu Tyr Ser Val Ala Met Tyr Gly Gly Leu Val Leu Phe Ser
 275 280 285

atg ttc ctt ctg tat gat acc cag aaa gta atc aag cgt gca gaa gta
 Met Phe Leu Leu Tyr Asp Thr Gln Lys Val Ile Lys Arg Ala Glu Val
 290 295 300

tca cca atg tat gga gtt caa aaa tat gat ccc att aac tcg atg ctg
 Ser Pro Met Tyr Gly Val Gln Lys Tyr Asp Pro Ile Asn Ser Met Leu
 305 310 315 320

agt atc tac atg gat aca tta aat ata ttt atg cga gtt gca act atg
 Ser Ile Tyr Met Asp Thr Leu Asn Ile Phe Met Arg Val Ala Thr Met
 325 330 335

ctg gca act gga ggc aac aga aag aaa tga
 Leu Ala Thr Gly Gly Asn Arg Lys Lys
 340 345

<210> 17
 <211> 345
 <212> PRT
 <213> Homo sapiens

<400> 17
 Met Leu Ala Ala Arg Leu Val Cys Leu Arg Thr Leu Pro Ser Arg Val
 1 5 10 15

Phe His Pro Ala Phe Thr Lys Ala Ser Pro Val Val Lys Asn Ser Ile
 20 25 30

Thr Lys Asn Gln Trp Leu Leu Thr Pro Ser Arg Glu Tyr Ala Thr Lys
 35 40 45

Thr Arg Ile Gly Ile Arg Arg Gly Arg Thr Gly Gln Glu Leu Lys Glu
 50 55 60

Ala Ala Leu Glu Pro Ser Met Glu Lys Ile Phe Lys Ile Asp Gln Met
 65 70 75 80

Gly Arg Trp Phe Val Ala Gly Gly Ala Ala Val Gly Leu Gly Ala Leu
 85 90 95

Cys Tyr Tyr Gly Leu Gly Leu Ser Asn Glu Ile Gly Ala Ile Glu Lys

100

105

110

Ala Val Ile Trp Pro Gln Tyr Val Lys Asp Arg Ile His Ser Thr Tyr
 115 120 125

Met Tyr Leu Ala Gly Ser Ile Gly Leu Thr Ala Leu Ser Ala Ile Ala
 130 135 140

Ile Ser Arg Thr Pro Val Leu Met Asn Phe Met Met Arg Gly Ser Trp
 145 150 155 160

Val Thr Ile Gly Val Thr Phe Ala Ala Met Val Gly Ala Gly Met Leu
 165 170 175

Val Arg Ser Ile Pro Tyr Asp Gln Ser Pro Gly Pro Lys His Leu Ala
 180 185 190

Trp Leu Leu His Ser Gly Val Met Gly Ala Val Val Ala Pro Leu Thr
 195 200 205

Ile Leu Gly Gly Pro Leu Leu Ile Arg Ala Ala Trp Tyr Thr Ala Gly
 210 215 220

Ile Val Gly Gly Leu Ser Thr Val Ala Met Cys Ala Pro Ser Glu Lys
 225 230 235 240

Phe Leu Asn Met Gly Ala Pro Leu Gly Val Gly Leu Gly Leu Val Phe
 245 250 255

Val Ser Ser Leu Gly Ser Met Phe Leu Pro Pro Thr Thr Val Ala Gly
 260 265 270

Ala Thr Leu Tyr Ser Val Ala Met Tyr Gly Gly Leu Val Leu Phe Ser
 275 280 285

Met Phe Leu Leu Tyr Asp Thr Gln Lys Val Ile Lys Arg Ala Glu Val
 290 295 300

Ser Pro Met Tyr Gly Val Gln Lys Tyr Asp Pro Ile Asn Ser Met Leu
 305 310 315 320

Ser Ile Tyr Met Asp Thr Leu Asn Ile Phe Met Arg Val Ala Thr Met

325

330

335

Leu Ala Thr Gly Gly Asn Arg Lys Lys
340 345

<210> 18
<211> 447
<212> DNA
<213> *Mus musculus*

<220>
<221> CDS
<222> (1)..(444)

<400> 18
atg agc acc tcg tct gcg cgg cct gca gtc ctg gcc ctt gcc ggg ctg
Met Ser Thr Ser Ser Ala Arg Pro Ala Val Leu Ala Leu Ala Gly Leu
1 5 10 15

gct ctg ctc ctt ctg ctg tgc ctg ggt cca gat ggc ata agt gga aac
Ala Leu Leu Leu Leu Leu Cys Leu Gly Pro Asp Gly Ile Ser Gly Asn
20 25 30

aaa ctc aag aag atg ctc cag aaa cga gaa gga cct gtc ccg tca aag
 Lys Leu Lys Lys Met Leu Gln Lys Arg Glu Gly Pro Val Pro Ser Lys
 35 40 45

act	aat	gta	gct	gta	gcc	gag	aac	aca	gca	aag	gaa	ttc	cta	ggt	ggc
Thr	Asn	Val	Ala	Val	Ala	Glu	Asn	Thr	Ala	Lys	Glu	Phe	Leu	Gly	Gly
50						55						60			

ctg aag cgt gcc aaa cga cag ctg tgg gac cgt acg cgg cct gag gta
 Leu Lys Arg Ala Lys Arg Gln Leu Trp Asp Arg Thr Arg Pro Glu Val
 65 70 75 80

cag cag tgg tac cag cag ttc ctc tac atg ggc ttt gat gag gct aaa
 Gln Gln Trp Tyr Gln Gln Phe Leu Tyr Met Gly Phe Asp Glu Ala Lys
 85 90 95

ttt gaa gat gat gtc aac tat tgg cta aac aga aat cga aac ggc cat
 Phe Glu Asp Asp Val Asn Tyr Trp Leu Asn Arg Asn Arg Asn Gly His
 100 105 110

gac tac tat ggt gac tac tac cag cgt cat tat gat gaa gat gcg gcc
 Asp Tyr Tyr Gly Asp Tyr Tyr Gln Arg His Tyr Asp Glu Asp Ala Ala
 115 120 125

att ggt ccc cac agc cgg gaa agc ttc agg cat gga gcc agt gtg aac
 Ile Gly Pro His Ser Arg Glu Ser Phe Arg His Gly Ala Ser Val Asn
 130 135 140

tat gat gac tat taa 447
Tyr Asp Asp Tyr
145

<210> 19
 <211> 148
 <212> PRT
 <213> *Mus musculus*

<400> 19
 Met Ser Thr Ser Ser Ala Arg Pro Ala Val Leu Ala Leu Ala Gly Leu
 1 5 10 15

Ala Leu Leu Leu Leu Cys Leu Gly Pro Asp Gly Ile Ser Gly Asn
 20 25 30

Lys Leu Lys Lys Met Leu Gln Lys Arg Glu Gly Pro Val Pro Ser Lys
 35 40 45

Thr Asn Val Ala Val Ala Glu Asn Thr Ala Lys Glu Phe Leu Gly Gly
 50 55 60

Leu Lys Arg Ala Lys Arg Gln Leu Trp Asp Arg Thr Arg Pro Glu Val
 65 70 75 80

Gln Gln Trp Tyr Gln Gln Phe Leu Tyr Met Gly Phe Asp Glu Ala Lys
 85 90 95

Phe Glu Asp Asp Val Asn Tyr Trp Leu Asn Arg Asn Arg Asn Gly His
 100 105 110

Asp Tyr Tyr Gly Asp Tyr Tyr Gln Arg His Tyr Asp Glu Asp Ala Ala
 115 120 125

Ile Gly Pro His Ser Arg Glu Ser Phe Arg His Gly Ala Ser Val Asn
 130 135 140

Tyr Asp Asp Tyr
 145

<210> 20
 <211> 447
 <212> DNA
 <213> *Homo sapiens*

<220>
 <221> CDS
 <222> (1)..(444)

<400> 20

atg gct gcc tcc ccc gcg cgg cct gct gtc ctg gcc ctg acc ggg ctg
 Met Ala Ala Ser Pro Ala Arg Pro Ala Val Leu Ala Leu Thr Gly Leu
 1 5 10 15

48

gcg ctg ctc ctg ctc ctg tgc tgg ggc cca ggt ggc ata agt gga aat
 Ala Leu Leu Leu Leu Cys Trp Gly Pro Gly Gly Ile Ser Gly Asn
 20 25 30

96

aaa ctc aag ctg atg ctt caa aaa cga gaa gca oct gtt cca act aag
 Lys Leu Lys Leu Met Leu Gln Lys Arg Glu Ala Pro Val Pro Thr Lys
 35 40 45

144

act aaa gtg gcc gtt gat gag aat aaa gcc aaa gaa ttc ctt ggc agc
 Thr Lys Val Ala Val Asp Glu Asn Lys Ala Lys Glu Phe Leu Gly Ser
 50 55 60

192

ctg aag cgc cag aag cgg cag ctg tgg gac cgg act cgg ccc gag gtg
 Leu Lys Arg Gln Lys Arg Gln Leu Trp Asp Arg Thr Arg Pro Glu Val
 65 70 75 80

240

cag cag tgg tac cag cag ttt ctc tac atg ggc ttt gac gaa gcg aaa
 Gln Gln Trp Tyr Gln Gln Phe Leu Tyr Met Gly Phe Asp Glu Ala Lys
 85 90 95

288

ttt gaa gat gac atc acc tat tgg ctt aac aga gat cga aat gga cat
 Phe Glu Asp Asp Ile Thr Tyr Trp Leu Asn Arg Asp Arg Asn Gly His
 100 105 110

336

gaa tac tat ggc gat tac tac caa cgt cac tat gat gaa gac tct gca
 Glu Tyr Gly Asp Tyr Tyr Gln Arg His Tyr Asp Glu Asp Ser Ala
 115 120 125

384

att ggt ccc cgg agc ccc tac ggc ttt agg cat gga gcc agc gtc aac
 Ile Gly Pro Arg Ser Pro Tyr Gly Phe Arg His Gly Ala Ser Val Asn
 130 135 140

432

tac gat gac tac taa
 Tyr Asp Asp Tyr
 145

447

<210> 21

<211> 148

<212> PRT

<213> Homo sapiens

<400> 21

Met Ala Ala Ser Pro Ala Arg Pro Ala Val Leu Ala Leu Thr Gly Leu
 1 5 10 15

Ala Leu Leu Leu Leu Cys Trp Gly Pro Gly Gly Ile Ser Gly Asn
 20 25 30

Lys Leu Lys Leu Met Leu Gln Lys Arg Glu Ala Pro Val Pro Thr Lys
 35 40 45

Thr Lys Val Ala Val Asp Glu Asn Lys Ala Lys Glu Phe Leu Gly Ser
 50 55 60

Leu Lys Arg Gln Lys Arg Gln Leu Trp Asp Arg Thr Arg Pro Glu Val
 65 70 75 80

Gln Gln Trp Tyr Gln Gln Phe Leu Tyr Met Gly Phe Asp Glu Ala Lys
 85 90 95

Phe Glu Asp Asp Ile Thr Tyr Trp Leu Asn Arg Asp Arg Asn Gly His
 100 105 110

Glu Tyr Tyr Gly Asp Tyr Tyr Gln Arg His Tyr Asp Glu Asp Ser Ala
 115 120 125

Ile Gly Pro Arg Ser Pro Tyr Gly Phe Arg His Gly Ala Ser Val Asn
 130 135 140

Tyr Asp Asp Tyr
 145

<210> 22
 <211> 3132
 <212> DNA
 <213> *Mus musculus*

<220>
 <221> CDS
 <222> (630)..(1358)

<400> 22		
gggggtctgc atctccatcg gaaagtgcgc tggccacatc cttccggcct cgggcagtg	60	
ttctgtctcc cttagctcgag gcagcgagaa acttcagctg tgaagtggtg gtggagagag	120	
ccctgggagc agcgactgga ccggacacc aagaagagag tggacgcgc cctcgactag	180	
aatcgctct cgcaggcgga gaccagcat ctcagcgctt ggggtcgcc ttgcggcc	240	
gcccgcgttt gctaggcgcc gccggcccg aaggacccctc ggggtcgcc gacccttcg	300	
cagccggcgaa atoctaaag ctgcggcccg aaggacccctc ggggtcgcc gacccttcg	360	
agcccaacgtg ctgaccacaaac agccggctc gcttccagag octggcatgg agccggcgcc	420	

Ile Pro Cys Pro Thr Ile Ala Glu Ser Arg Arg Cys Lys Met Ala Met				
185	190	195	200	
agg cac tgt cca gga gga aag aca aca aag gca aaa gag aag aca				1277
Arg His Cys Pro Gly Gly Lys Arg Thr Pro Lys Ala Lys Glu Lys Arg				
205	210	215		
aac aag aag aag agg cgg aag ctg att gag aca gac aac caa gag cag cac				1325
Asn Lys Lys Lys Arg Arg Lys Leu Ile Glu Arg Ala Gln Glu Gln His				
220	225	230		
agc gtc ttc ctc gct aca gac aca gtg aac caa taaaatacaa gaaaatagctg				1378
Ser Val Phe Leu Ala Thr Asp Arg Val Asn Gln				
235	240			
ggcattttg aggtttctg tttgtttat gttgtgtt tgcaaaagtg cacaaggta				1438
ctctccatgc cacactggtg gacagcattc ctgatccct gaccgtatc cattttcagt				1498
aatgctgcag agggaggtgc ccaagcatgg actcagcggtt atttatgctt tgattggaaat				1558
ctggggcctg tcatggcagg agcttgtga gctgagtcag cgggagctga tgcacatgt				1618
ctcttgat gggcacatgt tgctataaga acctgtccct ggcacgggtgg acccacagga				1678
ggcacaaggc ttagatcac caccagagaa tgcacatgtg cctatggta tggatggcaa				1738
tgctaagcaa gcaaggactg ttcaattgtg actttcattt ctcacactgt gcactgtcaa				1798
agacaaatgt gcatggaaaa atgtttatgt tcacatcatg gctgttcag catcagtgtac				1858
cttcaaaacgg tcctacaatg agactgtgtt ctatgtggg gtatgtgtg gaaattccctg				1918
ctacatttca tcttagtgat aacatgtaca gattctgtcg cgctacattt aaagcttatt				1978
actgtatatt tatgtttctt ctgtgtaca agttataacct gataagatgt cactttgttt				2038
ctatgttttc ttaaccatgg tctgttacat ggctattcta gttttggaaa ttaacaatgt				2098
ttttgttgc ttttttttc tttttttctt atcatttttgc ggggggttg ggtggcttg				2158
attctaaacgg taagtatagg ataagctatgt ttgttatata gaggtaatgt actgtatgtca				2218
gaggatcatgt gctgtatggaa ctcccccagt tcatgtcacg atacacacag agagaaagca				2278
gcatgaggca tcttgcattc agaagccaaa tttcttttgc gtccaaaaat tcatgtactta				2338
tgaaatatacg ctgaaaacaa gattgggtg tagttacttg tattttattt acaatttcca				2398
attacatttt ttttcaaact caaaataacc catgactttg agtgtatggt cacttggcaa				2458
tgttcttgc ttactggggaa agctgtgtc actaagataa tgagagagaa aatagaatgg				2518
cttcgcacaa gtgagagcca catcttacat ttctctgttg aatcgaaatc aactatattt				2578
gaacagaagc ctgatagaag ctttcttagtt aacacacaca aggccatggt ttcaaaaaca				2638

tctttgtccc	cttaggtcag	tttgcctta	gattatgaat	tggcagggttc	taattgcatt	2698
atttcoctgg	ctgatccagg	aaaaagttag	aacaaaataa	gttgcatagt	tttgaggaaa	2758
catccaaagc	aaggcgaagc	ctttccttgc	cttgcatgg	caaaaactacc	tcttagcat	2818
ttatgttgc	tcaaaaaat	cttgctgata	tgtgttagatg	tttttagctt	cattgtgaaa	2878
atattgtgc	aagataagcc	atataatgaat	gttgtattca	actttaggc	ttgaaattaa	2938
toctaaatgt	ttcacccctc	tocatgtcta	tttacactct	gttccattt	actaagaggg	2998
taggggtctc	cttaatatca	tacttcattg	ttaataagtc	aatgcttggtt	atgtttcttg	3058
gctgttgg	ttgtgcatta	aaaactcaaa	attggaaaaa	aaaaaaaaaa	aaaaaaaaaa	3118
aaaaaaaaaa	aaaa					3132

<210> 23

<211> 243

<212> PRT

<213> Mus musculus

<400> 23

Met	Arg	Phe	Cys	Leu	Phe	Ser	Phe	Ala	Leu	Ile	Ile	Leu	Asn	Cys	Met
1															15

Asp	Tyr	Ser	Gln	Cys	Gln	Gly	Asn	Arg	Trp	Arg	Arg	Asn	Lys	Arg	Ala
20															30

Ser	Tyr	Val	Ser	Asn	Pro	Ile	Cys	Lys	Gly	Cys	Leu	Ser	Cys	Ser	Lys
35															45

Asp	Asn	Gly	Cys	Ser	Arg	Cys	Gln	Gln	Lys	Leu	Phe	Phe	Phe	Leu	Arg
50															60

Arg	Glu	Gly	Met	Arg	Gln	Tyr	Gly	Glu	Cys	Leu	His	Ser	Cys	Pro	Ser
65															80

Gly	Tyr	Tyr	Gly	His	Arg	Ala	Pro	Asp	Met	Asn	Arg	Cys	Ala	Arg	Cys
85															95

Arg	Ile	Glu	Asn	Cys	Asp	Ser	Cys	Phe	Ser	Lys	Asp	Phe	Cys	Thr	Lys
100															110

Cys	Lys	Val	Gly	Phe	Tyr	Leu	His	Arg	Gly	Arg	Cys	Phe	Asp	Glu	Cys
115															125

Pro Asp Gly Phe Ala Pro Leu Asp Glu Thr Met Glu Cys Val Glu Gly
 130 135 140

Cys Glu Val Gly His Trp Ser Glu Trp Gly Thr Cys Ser Arg Asn Asn
 145 150 155 160

Arg Thr Cys Gly Phe Lys Trp Gly Leu Glu Thr Arg Thr Arg Gln Ile
 165 170 175

Val Lys Lys Pro Ala Lys Asp Thr Ile Pro Cys Pro Thr Ile Ala Glu
 180 185 190

Ser Arg Arg Cys Lys Met Ala Met Arg His Cys Pro Gly Gly Lys Arg
 195 200 205

Thr Pro Lys Ala Lys Glu Lys Arg Asn Lys Lys Arg Arg Lys Leu
 210 215 220

Ile Glu Arg Ala Gln Glu Gln His Ser Val Phe Leu Ala Thr Asp Arg
 225 230 235 240

Val Asn Gln

<210> 24
 <211> 843
 <212> DNA
 <213> *Mus musculus*

<220>
 <221> CDS
 <222> (132)..(506)

<400> 24
 ggccattatg gocggggct ttccgggtcc gggagctgac cggccgtgtt octctctgt 60
 cttoctctgc gocccgcgtc cccggccctcg cgaccggcgc tctccgtggac tggcgccgc 120
 caaccctgggc g atg ccc cgc tac gag ttg gct ttg att ctg aaa gcc atg 170
 Met Pro Arg Tyr Glu Leu Ala Leu Ile Leu Lys Ala Met
 1 5 10

cgg cgg cca gag acc gct gct gct ttg aaa cgt aca ata gaa tcc ctg 218
 Arg Arg Pro Glu Thr Ala Ala Leu Lys Arg Thr Ile Glu Ser Leu
 15 20 25

atg gac cga gga gcc ata gtg agg aac ttg gaa agc ctg ggt gag cgt Met Asp Arg Gly Ala Ile Val Arg Asn Leu Glu Ser Leu Gly Glu Arg 30 35 40 45	266
gct ctc ccc tac agg atc tcg agt cac agc cag cag cac agc cga gga Ala Leu Pro Tyr Arg Ile Ser Ser His Ser Gln Gln His Ser Arg Gly 50 55 60	314
ggg tat ttc ctg gtg gat ttt tat gct cgg aca agt gct gtg gag aac Gly Tyr Phe Leu Val Asp Phe Tyr Ala Pro Thr Ser Ala Val Glu Asn 65 70 75	362
ata ctg gaa cac ttg gcg cga gac att gac gtg gtt aga cca aat att Ile Leu Glu His Leu Ala Arg Asp Ile Asp Val Val Arg Pro Asn Ile 80 85 90	410
gtg aaa cac cct ctg acc cag gaa gta aaa gag tgt gac ggc ata gtc Val Lys His Pro Leu Thr Gln Glu Val Lys Glu Cys Asp Gly Ile Val 95 100 105	458
cca gtc cca ctt gaa gaa aaa ctg tat tca aca aag agg agg aag aag Pro Val Pro Leu Glu Glu Lys Leu Tyr Ser Thr Lys Arg Arg Lys Lys 110 115 120 125	506
tgagaagatt caccagattc tggccttata ttaatcta agggcactat gggtgctgt agttgtgt cttagatact tttagccatg accattttgc tgcaggaggt agaaactgt ggccgagacc tgccctgatg tctctgtga gatttcatcc cacttgtggg gtttgcgg agtgggggtg ttcacagtac cactgttagcg tttccaagag caaaatgttt gtcattcaca cttggttgtc ttgcaagct atatgaaaca ctgggagcag agtaataaac atgactttat caacaactgga aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 843	566 626 686 746 806

<210> 25
 <211> 125
 <212> PRT
 <213> Mus musculus

<400> 25
 Met Pro Arg Tyr Glu Leu Ala Leu Ile Leu Lys Ala Met Arg Arg Pro
 1 5 10 15

Glu Thr Ala Ala Ala Leu Lys Arg Thr Ile Glu Ser Leu Met Asp Arg
 20 25 30

Gly Ala Ile Val Arg Asn Leu Glu Ser Leu Gly Glu Arg Ala Leu Pro
 35 40 45

Tyr Arg Ile Ser Ser His Ser Gln Gln His Ser Arg Gly Gly Tyr Phe

50 55 60

Leu Val Asp Phe Tyr Ala Pro Thr Ser Ala Val Glu Asn Ile Leu Glu
 65 70 75 80

His Leu Ala Arg Asp Ile Asp Val Val Arg Pro Asn Ile Val Lys His
 85 90 95

Pro Leu Thr Gln Glu Val Lys Glu Cys Asp Gly Ile Val Pro Val Pro
 100 105 110

Leu Glu Glu Lys Leu Tyr Ser Thr Lys Arg Arg Lys Lys
 115 120 125

<210> 26

<211> 2490

<212> DNA

<213> *Mus musculus*

<220>

<221> CDS

<222> (1)..(2487)

<400> 26

atg aag ccg ccc ggc agc atc tcc cgg cgg ccg acc ctg acg ggt tgc
 Met Lys Pro Pro Gly Ser Ile Ser Arg Arg Pro Thr Leu Thr Gly Cys
 1 5 10 15

agc ctt ccc ggc gcc tcc tgc ggc ccc ggc cgc tgc ccc gcc ggc ccg
 Ser Leu Pro Gly Ala Ser Cys Gly Pro Gly Arg Cys Pro Ala Gly Pro
 20 25 30

gtg ccg gcc cgc gcg ccc tgc cgc ctg ctc ctc gtc ctt ctc ctg
 Val Pro Ala Arg Ala Pro Pro Cys Arg Leu Leu Leu Val Leu Leu Leu
 35 40 45

cta cct gcg ctc gcc acc tca tcc cgg ccc cgt gcc cgg ggg gcc gct
 Leu Pro Ala Leu Ala Thr Ser Ser Arg Pro Arg Ala Arg Gly Ala Ala
 50 55 60

gcg ccc agc gct ccg cac tgg aat gaa act gca gaa aaa acc ctg gga
 Ala Pro Ser Ala Pro His Trp Asn Glu Thr Ala Glu Lys Thr Leu Gly
 65 70 75 80

gtc ctg gca gat gaa gac aac aca ttg caa caa aat agc agc agc aga
 Val Leu Ala Asp Glu Asp Asn Thr Leu Gln Gln Asn Ser Ser Ser Arg
 85 90 95

aat acc agc tac agc agt gca gtg caa aaa gaa atc aca ctg cct tca
 Asn Thr Ser Tyr Ser Ser Ala Val Gln Lys Glu Ile Thr Leu Pro Ser
 100 105 110

48

96

144

192

240

288

336

aga ctg gtg tat tac atc aac cag gac tca gaa agc ccc tat cat gtt Arg Leu Val Tyr Tyr Ile Asn Gln Asp Ser Glu Ser Pro Tyr His Val 115 120 125	384
ctt gac aca aag gcc aga cac caa cag aaa cac aat aag gct gtg cat Leu Asp Thr Lys Ala Arg His Gln Gln Lys His Asn Lys Ala Val His 130 135 140	432
ctg gcc cag gca agc ttc cag atc gaa gct ttc ggc tcc aag ttc att Leu Ala Gln Ala Ser Phe Gln Ile Glu Ala Phe Gly Ser Lys Phe Ile 145 150 155 160	480
ctt gac ctc aca ctg aac aat ggt ttg cta tct tct gac tac gtg gag Leu Asp Leu Thr Leu Asn Asn Gly Leu Leu Ser Ser Asp Tyr Val Glu 165 170 175	528
atc cac tat gaa gac ggg aag cag atg tac tct aag ggt gga gag cac Ile His Tyr Glu Asp Gly Lys Gln Met Tyr Ser Lys Gly Gly Glu His 180 185 190	576
tgt tac tac cac gga agc atc aga ggc gtc aag gat tcc agg gtg gct Cys Tyr Tyr His Gly Ser Ile Arg Gly Val Lys Asp Ser Arg Val Ala 195 200 205	624
cta tcg acc tgc aat gga ctc cat ggc atg ttt gag gat gac acc ttt Leu Ser Thr Cys Asn Gly Leu His Gly Met Phe Glu Asp Asp Thr Phe 210 215 220	672
gtg tat atg ata gag cct ctg gaa ctg act gat gat gag aaa agc aca Val Tyr Met Ile Glu Pro Leu Glu Leu Thr Asp Asp Glu Lys Ser Thr 225 230 235 240	720
ggc cga ccg cac ata atc cag aaa acc ttg gca gga cag tat tct aag Gly Arg Pro His Ile Ile Gln Lys Thr Leu Ala Gly Gln Tyr Ser Lys 245 250 255	768
cag atg aag aat ctc agc aca gat ggc agt gac cag tgg cct ttg cta Gln Met Lys Asn Leu Ser Thr Asp Gly Ser Asp Gln Trp Pro Leu Leu 260 265 270	816
cct gaa tta caa tgg ctg aga aga agg aaa aga gcg gtc aat cca tct Pro Glu Leu Gln Trp Leu Arg Arg Lys Arg Ala Val Asn Pro Ser 275 280 285	864
cgt ggt gtg ttt gaa gaa atg aag tat ttg gag ctt atg att gtt aat Arg Gly Val Phe Glu Glu Met Lys Tyr Leu Glu Leu Met Ile Val Asn 290 295 300	912
gat cac aag acg tat aag aag cac cgc tct tct cac ggc cat acc aac Asp His Lys Thr Tyr Lys Lys His Arg Ser Ser His Ala His Thr Asn 305 310 315 320	960
aac ttc gca aag tct gtg gtc aac ctt gta gat tct att tac aag gaa Asn Phe Ala Lys Ser Val Val Asn Leu Val Asp Ser Ile Tyr Lys Glu 325 330 335	1008

cag ctc aac acc agg gtt gtc ctg gtg gct gtc gag acc tgg acc gag Gln Leu Asn Thr Arg Val Val Leu Val Ala Val Glu Thr Trp Thr Glu 340 345 350	1056
aag gat cac att gac atc acc atc aac ccc gtg cag atg cta cat gac Lys Asp His Ile Asp Ile Thr Ile Asn Pro Val Gln Met Leu His Asp 355 360 365	1104
ttc tcc aag tac cgg cag cga atc aaa cag cac gct gac gcg gtc cac Phe Ser Lys Tyr Arg Gln Arg Ile Lys Gln His Ala Asp Ala Val His 370 375 380	1152
ctc atc tcg cgc gtg aca ttc cat tat aag aga agc agt ctg agt tac Leu Ile Ser Arg Val Thr Phe His Tyr Lys Arg Ser Ser Leu Ser Tyr 385 390 395 400	1200
ttt gga ggc gtg tgt tct cga ata aga ggg gtt ggt gtg aat gag tat Phe Gly Gly Val Cys Ser Arg Ile Arg Gly Val Gly Val Asn Glu Tyr 405 410 415	1248
ggt ctt cca atg gcg gtg gca caa gta tta tca cag agc ctg gct caa Gly Leu Pro Met Ala Val Ala Gln Val Leu Ser Gln Ser Leu Ala Gln 420 425 430	1296
aac ctt gga atc cag tgg gaa cct tcg agc agg aag cca aaa tgt gaa Asn Leu Gly Ile Gln Trp Glu Pro Ser Ser Arg Lys Pro Lys Cys Glu 435 440 445	1344
tgc ata gag tcc tgg ggc ggc tgc atc atg gaa gaa aca ggg gtg tcc Cys Ile Glu Ser Trp Gly Gly Cys Ile Met Glu Glu Thr Gly Val Ser 450 455 460	1392
cac tct cga aag ttc tca aag tgc agc att ttg gag tac aga gac ttt His Ser Arg Lys Phe Ser Lys Cys Ser Ile Leu Glu Tyr Arg Asp Phe 465 470 475 480	1440
tta cag aga ggt ggc gga gca tgt ctt ttc aat agg cca act aag ctg Leu Gln Arg Gly Gly Ala Cys Leu Phe Asn Arg Pro Thr Lys Leu 485 490 495	1488
ttt gag ccc acg gaa tgt gga aat gga tat gtg gag gcc ggg gag gaa Phe Glu Pro Thr Glu Cys Gly Asn Gly Tyr Val Glu Ala Gly Glu Glu 500 505 510	1536
tgc gac tgt ggt ttc cat gtg gaa tgc tat gga gtt tgc tgt aag aag Cys Asp Cys Gly Phe His Val Glu Cys Tyr Gly Val Cys Cys Lys Lys 515 520 525	1584
tgt tgc ctc tcc aat ggg gcc cac tgc agt gac ggc ccc tgc tgt aac Cys Ser Leu Ser Asn Gly Ala His Cys Ser Asp Gly Pro Cys Cys Asn 530 535 540	1632
aac acc tca tgt ctt ttt cag tca cga ggg tat gaa tgt cgg gat gcc Asn Thr Ser Cys Leu Phe Gln Ser Arg Gly Tyr Glu Cys Arg Asp Ala 545 550 555 560	1680

gta aac agc tgt gat atc acc gag tac tgc act gga gac tct ggc cag Val Asn Ser Cys Asp Ile Thr Glu Tyr Cys Thr Gly Asp Ser Gly Gln 565 570 575	1728
tgc cca ccg aac ctc cat aaa caa gat ggc tat agc tgc aat caa aat Cys Pro Pro Asn Leu His Lys Gln Asp Gly Tyr Ser Cys Asn Gln Asn 580 585 590	1776
cag ggt cgc tgc tac aat ggc gag tgc aag aca agg gac aat caa tgc Gln Gly Arg Cys Tyr Asn Gly Glu Cys Lys Thr Arg Asp Asn Gln Cys 595 600 605	1824
cag tac atc tgg ggg aca aag gct gcg ggg tca gac aag ttc tgc tat Gln Tyr Ile Trp Gly Thr Lys Ala Ala Gly Ser Asp Lys Phe Cys Tyr 610 615 620	1872
gaa aag ctg aac acg gaa ggc acc gag aag ggc aat tgt gga aag gat Glu Lys Leu Asn Thr Glu Gly Thr Glu Lys Gly Asn Cys Gly Lys Asp 625 630 635 640	1920
gga gac cgg tgg atc ccg tgc agc aag cat gat gtg ttc tgt gga ttt Gly Asp Arg Trp Ile Pro Cys Ser Lys His Asp Val Phe Cys Gly Phe 645 650 655	1968
ctg ctt tgc acc aat ctt acc cga gct cca cgt atc ggt caa ctt caa Leu Leu Cys Thr Asn Leu Thr Arg Ala Pro Arg Ile Gly Gln Leu Gln 660 665 670	2016
gga gag atc atc ccg act tcc ttc tat cat caa ggc cga gtg att gac Gly Glu Ile Ile Pro Thr Ser Phe Tyr His Gln Gly Arg Val Ile Asp 675 680 685	2064
tgc agt ggt gct cat gta gtt tta gac gat gat aca gac gtg ggt tac Cys Ser Gly Ala His Val Val Leu Asp Asp Asp Thr Asp Val Gly Tyr 690 695 700	2112
gtt gaa gat ggg act ccg tgt ggc ccc tcc atg atg tgc tta gat cgg Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys Leu Asp Arg 705 710 715 720	2160
aag tgc cta cag att caa gcc ctg aat atg agc agc tgc cca ctt gac Lys Cys Leu Gln Ile Gln Ala Leu Asn Met Ser Ser Cys Pro Leu Asp 725 730 735	2208
tca agg ggt aaa gtc tgc toc ggc cac ggg gtg tgt agc aac gaa gcc Ser Arg Gly Lys Val Cys Ser Gly His Gly Val Cys Ser Asn Glu Ala 740 745 750	2256
acc tgc atc tgt gat ttc act tgg gca ggc aca gac tgc agc atc cgg Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys Ser Ile Arg 755 760 765	2304
gat cca gtt cgg aac ccc aac ccc cct aag gat gaa ggc cct aag ggt Asp Pro Val Arg Asn Pro Asn Pro Lys Asp Glu Gly Pro Lys Gly 770 775 780	2352

cct agc gcc acc aat ctc ata ata ggc tcc atc gct ggt gcc atc ctg Pro Ser Ala Thr Asn Leu Ile Ile Gly Ser Ile Ala Gly Ala Ile Leu 785 790 795 800	2400
gta gca gct att gtc ctt ggg ggc aca ggc tgg gga ttt aaa aac gtc Val Ala Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Val 805 810 815	2448
aag aag agg aga ttc gat ccc act cag caa ggc ccc atc tga Lys Lys Arg Arg Phe Asp Pro Thr Gln Gln Gly Pro Ile 820 825	2490
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Ser Leu Pro Gly Ala Ser Cys Gly Pro Gly Arg Cys Pro Ala Gly Pro 20 25 30	
Val Pro Ala Arg Ala Pro Pro Cys Arg Leu Leu Leu Val Leu Leu Leu 35 40 45	
Leu Pro Ala Leu Ala Thr Ser Ser Arg Pro Arg Ala Arg Gly Ala Ala 50 55 60	
Ala Pro Ser Ala Pro His Trp Asn Glu Thr Ala Glu Lys Thr Leu Gly 65 70 75 80	
Val Leu Ala Asp Glu Asp Asn Thr Leu Gln Gln Asn Ser Ser Arg 85 90 95	
Asn Thr Ser Tyr Ser Ser Ala Val Gln Lys Glu Ile Thr Leu Pro Ser 100 105 110	
Arg Leu Val Tyr Tyr Ile Asn Gln Asp Ser Glu Ser Pro Tyr His Val 115 120 125	
Leu Asp Thr Lys Ala Arg His Gln Gln Lys His Asn Lys Ala Val His 130 135 140	

Leu Ala Gln Ala Ser Phe Gln Ile Glu Ala Phe Gly Ser Lys Phe Ile
 145 150 155 160

Leu Asp Leu Thr Leu Asn Asn Gly Leu Leu Ser Ser Asp Tyr Val Glu
 165 170 175

Ile His Tyr Glu Asp Gly Lys Gln Met Tyr Ser Lys Gly Gly Glu His
 180 185 190

Cys Tyr Tyr His Gly Ser Ile Arg Gly Val Lys Asp Ser Arg Val Ala
 195 200 205

Leu Ser Thr Cys Asn Gly Leu His Gly Met Phe Glu Asp Asp Thr Phe
 210 215 220

Val Tyr Met Ile Glu Pro Leu Glu Leu Thr Asp Asp Glu Lys Ser Thr
 225 230 235 240

Gly Arg Pro His Ile Ile Gln Lys Thr Leu Ala Gly Gln Tyr Ser Lys
 245 250 255

Gln Met Lys Asn Leu Ser Thr Asp Gly Ser Asp Gln Trp Pro Leu Leu
 260 265 270

Pro Glu Leu Gln Trp Leu Arg Arg Arg Lys Arg Ala Val Asn Pro Ser
 275 280 285

Arg Gly Val Phe Glu Glu Met Lys Tyr Leu Glu Leu Met Ile Val Asn
 290 295 300

Asp His Lys Thr Tyr Lys Lys His Arg Ser Ser His Ala His Thr Asn
 305 310 315 320

Asn Phe Ala Lys Ser Val Val Asn Leu Val Asp Ser Ile Tyr Lys Glu
 325 330 335

Gln Leu Asn Thr Arg Val Val Leu Val Ala Val Glu Thr Trp Thr Glu
 340 345 350

Lys Asp His Ile Asp Ile Thr Ile Asn Pro Val Gln Met Leu His Asp
 355 360 365

Phe Ser Lys Tyr Arg Gln Arg Ile Lys Gln His Ala Asp Ala Val His
370 375 380

Leu Ile Ser Arg Val Thr Phe His Tyr Lys Arg Ser Ser Leu Ser Tyr
385 390 395 400

Phe Gly Gly Val Cys Ser Arg Ile Arg Gly Val Gly Val Asn Glu Tyr
405 410 415

Gly Leu Pro Met Ala Val Ala Gln Val Leu Ser Gln Ser Leu Ala Gln
420 425 430

Asn Leu Gly Ile Gln Trp Glu Pro Ser Ser Arg Lys Pro Lys Cys Glu
435 440 445

Cys Ile Glu Ser Trp Gly Gly Cys Ile Met Glu Glu Thr Gly Val Ser
450 455 460

His Ser Arg Lys Phe Ser Lys Cys Ser Ile Leu Glu Tyr Arg Asp Phe
465 470 475 480

Leu Gln Arg Gly Gly Ala Cys Leu Phe Asn Arg Pro Thr Lys Leu
485 490 495

Phe Glu Pro Thr Glu Cys Gly Asn Gly Tyr Val Glu Ala Gly Glu Glu
500 505 510

Cys Asp Cys Gly Phe His Val Glu Cys Tyr Gly Val Cys Cys Lys Lys
515 520 525

Cys Ser Leu Ser Asn Gly Ala His Cys Ser Asp Gly Pro Cys Cys Asn
530 535 540

Asn Thr Ser Cys Leu Phe Gln Ser Arg Gly Tyr Glu Cys Arg Asp Ala
545 550 555 560

Val Asn Ser Cys Asp Ile Thr Glu Tyr Cys Thr Gly Asp Ser Gly Gln
565 570 575

Cys Pro Pro Asn Leu His Lys Gln Asp Gly Tyr Ser Cys Asn Gln Asn
580 585 590

Gln Gly Arg Cys Tyr Asn Gly Glu Cys Lys Thr Arg Asp Asn Gln Cys
 595 600 605

Gln Tyr Ile Trp Gly Thr Lys Ala Ala Gly Ser Asp Lys Phe Cys Tyr
 610 615 620

Glu Lys Leu Asn Thr Glu Gly Thr Glu Lys Gly Asn Cys Gly Lys Asp
 625 630 635 640

Gly Asp Arg Trp Ile Pro Cys Ser Lys His Asp Val Phe Cys Gly Phe
 645 650 655

Leu Leu Cys Thr Asn Leu Thr Arg Ala Pro Arg Ile Gly Gln Leu Gln
 660 665 670

Gly Glu Ile Ile Pro Thr Ser Phe Tyr His Gln Gly Arg Val Ile Asp
 675 680 685

Cys Ser Gly Ala His Val Val Leu Asp Asp Asp Thr Asp Val Gly Tyr
 690 695 700

Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys Leu Asp Arg
 705 710 715 720

Lys Cys Leu Gln Ile Gln Ala Leu Asn Met Ser Ser Cys Pro Leu Asp
 725 730 735

Ser Arg Gly Lys Val Cys Ser Gly His Gly Val Cys Ser Asn Glu Ala
 740 745 750

Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys Ser Ile Arg
 755 760 765

Asp Pro Val Arg Asn Pro Asn Pro Pro Lys Asp Glu Gly Pro Lys Gly
 770 775 780

Pro Ser Ala Thr Asn Leu Ile Ile Gly Ser Ile Ala Gly Ala Ile Leu
 785 790 795 800

Val Ala Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Val
 805 810 815

Lys Lys Arg Arg Phe Asp Pro Thr Gln Gln Gly Pro Ile
820 825

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Met Lys Pro Pro Gly Ser Ser Arg Gln Pro Pro Leu Ala Gly Cys
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48

agc ctt gcc ggc gct tcc tgc ggc ccc caa cgc ggc ccc gcc ggc tgc
Ser Leu Ala Gly Ala Ser Cys Gly Pro Gln Arg Gly Pro Ala Gly Ser
20 25 30

96

gtg cct gcc agc gcc ccg cgc acg ccg ccc tgc cgc ctg ctt ctc
Val Pro Ala Ser Ala Pro Ala Arg Thr Pro Pro Cys Arg Leu Leu Leu
35 40 45

144

gtc ctt ctc ctg ctg cct ccg ctc gcc gcc tcg tcc cgg ccc cgc gcc
Val Leu Leu Leu Pro Pro Leu Ala Ala Ser Ser Arg Pro Arg Ala
50 55 60

192

tgg ggg gct gct gcg ccc agc gct cat tgg aat gaa act gca gaa
Trp Gly Ala Ala Ala Pro Ser Ala Pro His Trp Asn Glu Thr Ala Glu
65 70 75 80

240

aaa aat ttg gga gtc ctg gca gat gaa gac aat aca ttg caa cag aat
Lys Asn Leu Gly Val Leu Ala Asp Glu Asp Asn Thr Leu Gln Gln Asn
85 90 95

288

agc agc agt aat atc agt tac agc aat gca atg cag aaa gaa atc aca
Ser Ser Ser Asn Ile Ser Tyr Ser Asn Ala Met Gln Lys Glu Ile Thr
100 105 110

336

ctg cct tca aga ctc ata tat tac atc aac caa gac tcg gaa agc oct
Leu Pro Ser Arg Leu Ile Tyr Tyr Ile Asn Gln Asp Ser Glu Ser Pro
115 120 125

384

tat cac gtt ctt gac aca aag gca aga cac cag caa aaa cat aat aag
Tyr His Val Leu Asp Thr Lys Ala Arg His Gln Gln Lys His Asn Lys
130 135 140

432

gct gtc cat ctg gcc cag gca agc ttc cag att gaa gcc ttc ggc tcc
Ala Val His Leu Ala Gln Ala Ser Phe Gln Ile Glu Ala Phe Gly Ser
145 150 155 160

480

aaa ttc att ctt gac ctc ata ctg aac aat ggt ttg ttg tct tct gat
Lys Phe Ile Leu Asp Leu Ile Leu Asn Asn Gln Leu Leu Ser Ser Asp

528

	165	170	175	
tat gtg gag att cac tac gaa aat ggg aaa cca cag tac tct aag ggt Tyr Val Glu Ile His Tyr Glu Asn Gly Lys Pro Gln Tyr Ser Lys Gly	180	185	190	576
gga gag cac tgt tac tac cat gga agc atc aga ggc gtc aaa gac tcc Gly Glu His Cys Tyr His Gly Ser Ile Arg Gly Val Lys Asp Ser	195	200	205	624
aag gtg gct ctg tca acc tgc aat gga ctt cat ggc atg ttt gaa gat Lys Val Ala Leu Ser Thr Cys Asn Gly Leu His Gly Met Phe Glu Asp	210	215	220	672
gat acc ttc gtg tat atg ata gag cca cta gag ctg gtt cat gat gag Asp Thr Phe Val Tyr Met Ile Glu Pro Leu Glu Leu Val His Asp Glu	225	230	235	720
aaa agc aca ggt cga cca cat ata atc cag aaa acc ttg gca gga cag Lys Ser Thr Gly Arg Pro His Ile Ile Gln Lys Thr Leu Ala Gly Gln	245	250	255	768
tat tct aag caa atg aag aat ctc act atg gaa aga ggt gac cag tgg Tyr Ser Lys Gln Met Lys Asn Leu Thr Met Glu Arg Gly Asp Gln Trp	260	265	270	816
coc ttt ctc tct gaa tta cag tgg ttg aaa aga agg aag aga gca gtg Pro Phe Leu Ser Glu Leu Gln Trp Leu Lys Arg Arg Lys Arg Ala Val	275	280	285	864
aat cca tca cgt ggt ata ttt gaa gaa atg aaa tat ttg gaa ctt atg Asn Pro Ser Arg Gly Ile Phe Glu Glu Met Lys Tyr Leu Glu Leu Met	290	295	300	912
att gtt aat gat cac aaa acg tat aag aag cat cgc tct tct cat gca Ile Val Asn Asp His Lys Thr Tyr Lys His Arg Ser Ser His Ala	305	310	315	960
cat acc aac aac ttt gca aag tcc gtg gtc aac ctt gtg gat tct att His Thr Asn Asn Phe Ala Lys Ser Val Val Asn Leu Val Asp Ser Ile	325	330	335	1008
tac aag gag cag ctc aac acc agg gtt gtc ctg gtg gct gta gag acc Tyr Lys Glu Gln Leu Asn Thr Arg Val Val Leu Val Ala Val Glu Thr	340	345	350	1056
tgg act gag aag gat cag att gac atc acc aac cct gtg cag atg Trp Thr Glu Lys Asp Gln Ile Asp Ile Thr Thr Asn Pro Val Gln Met	355	360	365	1104
ctc cat gag ttc tca aaa tac cgg cag cgc att aag cag cat gct gat Leu His Glu Phe Ser Lys Tyr Arg Gln Arg Ile Lys Gln His Ala Asp	370	375	380	1152
gct gtg cac ctc atc tcg cgg gtg aca ttt cac tat aag aga agc agt Ala Val His Leu Ile Ser Arg Val Thr Phe His Tyr Lys Arg Ser Ser				1200

385	390	395	400														
ctg	agt	tac	ttt	gga	ggt	gtc	tgt	tct	cgc	aca	aga	gga	gtt	ggt	gtg		1248
Leu	Ser	Tyr	Phe	Gly	Gly	Val	Cys	Ser	Arg	Thr	Arg	Gly	Val	Gly	Val		
							405		410					415			
aat	gag	tat	ggt	ctt	cca	atg	gca	gtg	gca	caa	gta	tta	tgc	cag	agc		1296
Asn	Glu	Tyr	Gly	Leu	Pro	Met	Ala	Val	Ala	Gln	Val	Leu	Ser	Gln	Ser		
							420		425					430			
ctg	gct	caa	aac	ctt	gga	atc	caa	tgg	gaa	cct	tct	agc	aga	aag	cca		1344
Leu	Ala	Gln	Asn	Leu	Gly	Ile	Gln	Trp	Glu	Pro	Ser	Ser	Arg	Lys	Pro		
							435		440					445			
aaa	tgt	gac	tgc	aca	gaa	tcc	tgg	ggt	ggc	tgc	atc	atg	gag	gaa	aca		1392
Lys	Cys	Asp	Cys	Thr	Glu	Ser	Trp	Gly	Gly	Cys	Ile	Met	Glu	Glu	Thr		
							450		455					460			
ggg	gtg	tcc	cat	tct	cga	aaa	ttt	tca	aag	tgc	agc	att	ttg	gag	tat		1440
Gly	Val	Ser	His	Ser	Arg	Lys	Phe	Ser	Lys	Cys	Ser	Ile	Leu	Glu	Tyr		
							465		470					475		480	
aga	gac	ttt	tta	cag	aga	gga	ggt	gga	gcc	tgc	ctt	ttc	aac	agg	cca		1488
Arg	Asp	Phe	Leu	Gln	Arg	Gly	Gly	Gly	Ala	Cys	Leu	Phe	Asn	Arg	Pro		
							485		490					495			
aca	aag	cta	ttt	gag	ccc	acg	gaa	tgt	gga	aat	gga	tac	gtg	gaa	gct		1536
Thr	Lys	Leu	Phe	Glu	Pro	Thr	Glu	Cys	Gly	Asn	Gly	Tyr	Val	Glu	Ala		
							500		505					510			
ggg	gag	gag	tgt	gat	tgt	ggt	ttt	cat	gtg	gaa	tgc	tat	gga	tta	tgc		1584
Gly	Glu	Glu	Cys	Asp	Cys	Gly	Phe	His	Val	Glu	Cys	Tyr	Gly	Leu	Cys		
							515		520					525			
tgt	aag	aaa	tgt	tcc	ctc	tcc	aac	ggg	gct	cac	tgc	agc	gac	ggg	ccc		1632
Cys	Lys	Cys	Ser	Leu	Ser	Asn	Gly	Ala	His	Cys	Ser	Asp	Gly	Pro			
							530		535					540			
tgc	tgt	aac	aat	acc	tca	tgt	ctt	ttt	cag	cca	cga	ggg	tat	gaa	tgc		1680
Cys	Cys	Asn	Asn	Thr	Ser	Cys	Leu	Phe	Gln	Pro	Arg	Gly	Tyr	Glu	Cys		
							545		550					555		560	
cg	gat	gct	gtg	aac	gag	tgt	gat	att	act	gaa	tat	tgt	act	gga	gac		1728
Arg	Asp	Ala	Val	Asn	Glu	Cys	Asp	Ile	Thr	Glu	Tyr	Cys	Thr	Gly	Asp		
							565		570					575			
tct	ggt	cag	tgc	cca	cca	aat	ctt	cat	aag	caa	gac	gga	tat	gca	tgc		1776
Ser	Gly	Gln	Cys	Pro	Pro	Asn	Leu	His	Lys	Gln	Asp	Gly	Tyr	Ala	Cys		
							580		585					590			
aat	caa	aat	cag	ggc	cgc	tgc	tac	aat	ggc	gag	tgc	aag	acc	aga	gac		1824
Asn	Gln	Asn	Gln	Gly	Arg	Cys	Tyr	Asn	Gly	Glu	Cys	Lys	Thr	Arg	Asp		
							595		600					605			
aac	cag	tgt	cag	tac	atc	tgg	gga	aca	aag	gct	gca	ggg	tct	gac	aag		1872
Asn	Gln	Cys	Gln	Tyr	Ile	Trp	Gly	Thr	Lys	Ala	Ala	Gly	Ser	Asp	Lys		

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ggg aag gat gga gac cgg tgg att cag tgc agc aaa cat gat gtg ttc Gly Lys Asp Gly Asp Arg Trp Ile Gln Cys Ser Lys His Asp Val Phe 645 650 655			1968
tgt gga ttc tta ctc tgt acc aat ctt act cga gct cca cgt att ggt Cys Gly Phe Leu Leu Cys Thr Asn Leu Thr Arg Ala Pro Arg Ile Gly 660 665 670			2016
caa ctt cag ggt gag atc att cca act tcc ttc tac cat caa ggc cgg Gln Leu Gln Gly Glu Ile Ile Pro Thr Ser Phe Tyr His Gln Gly Arg 675 680 685			2064
gtg att gac tgc agt ggt gcc cat gta gtt tta gat gat gat acg gat Val Ile Asp Cys Ser Gly Ala His Val Val Leu Asp Asp Asp Thr Asp 690 695 700			2112
gtg ggc tat gta gaa gat gga acg cca tgt ggc cgg tct atg atg atg tgt Val Gly Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys 705 710 715 720			2160
tta gat cgg aag tgc cta caa att caa gcc cta aat atg agc agc tgt Leu Asp Arg Lys Cys Leu Gln Ile Gln Ala Leu Asn Met Ser Ser Cys 725 730 735			2208
cca ctc gat tcc aag ggt aaa gtc tgt tcg ggc cat ggg gtg tgt agt Pro Leu Asp Ser Lys Gly Lys Val Cys Ser Gly His Gly Val Cys Ser 740 745 750			2256
aat gaa gcc acc tgc att tgt gat ttc acc tgg gca ggg aca gat tgc Asn Glu Ala Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys 755 760 765			2304
agt atc cgg gat cca gtt agg aac ctt cac ccc ccc aag gat gaa gga Ser Ile Arg Asp Pro Val Arg Asn Leu His Pro Pro Lys Asp Glu Gly 770 775 780			2352
ccc aag ggt cct agt gcc acc aat ctc ata ata ggc tcc atc gct ggt Pro Lys Gly Pro Ser Ala Thr Asn Leu Ile Ile Gly Ser Ile Ala Gly 785 790 795 800			2400
gcc atc ctg gta gca gct att gtc ctt ggg ggc aca ggc tgg gga ttt Ala Ile Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe 805 810 815			2448
aaa aat gtc aag aag aga agg ttc gat cct act cag caa ggc ccc atc Lys Asn Val Lys Lys Arg Arg Phe Asp Pro Thr Gln Gln Gly Pro Ile 820 825 830			2496
tga			2499

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Val Pro Ala Ser Ala Pro Ala Arg Thr Pro Pro Cys Arg Leu Leu Leu
 35 40 45

Val Leu Leu Leu Leu Pro Pro Leu Ala Ala Ser Ser Arg Pro Arg Ala
 50 55 60

Trp Gly Ala Ala Ala Pro Ser Ala Pro His Trp Asn Glu Thr Ala Glu
 65 70 75 80

Lys Asn Leu Gly Val Leu Ala Asp Glu Asn Thr Leu Gln Gln Asn
 85 90 95

Ser Ser Ser Asn Ile Ser Tyr Ser Asn Ala Met Gln Lys Glu Ile Thr
 100 105 110

Leu Pro Ser Arg Leu Ile Tyr Tyr Ile Asn Gln Asp Ser Glu Ser Pro
 115 120 125

Tyr His Val Leu Asp Thr Lys Ala Arg His Gln Gln Lys His Asn Lys
 130 135 140

Ala Val His Leu Ala Gln Ala Ser Phe Gln Ile Glu Ala Phe Gly Ser
 145 150 155 160

Lys Phe Ile Leu Asp Leu Ile Leu Asn Asn Gly Leu Leu Ser Ser Asp
 165 170 175

Tyr Val Glu Ile His Tyr Glu Asn Gly Lys Pro Gln Tyr Ser Lys Gly
 180 185 190

Gly Glu His Cys Tyr Tyr His Gly Ser Ile Arg Gly Val Lys Asp Ser

195

200

205

Lys Val Ala Leu Ser Thr Cys Asn Gly Leu His Gly Met Phe Glu Asp
 210 215 220

Asp Thr Phe Val Tyr Met Ile Glu Pro Leu Glu Leu Val His Asp Glu
 225 230 235 240

Lys Ser Thr Gly Arg Pro His Ile Ile Gln Lys Thr Leu Ala Gly Gln
 245 250 255

Tyr Ser Lys Gln Met Lys Asn Leu Thr Met Glu Arg Gly Asp Gln Trp
 260 265 270

Pro Phe Leu Ser Glu Leu Gln Trp Leu Lys Arg Arg Lys Arg Ala Val
 275 280 285

Asn Pro Ser Arg Gly Ile Phe Glu Glu Met Lys Tyr Leu Glu Leu Met
 290 295 300

Ile Val Asn Asp His Lys Thr Tyr Lys Lys His Arg Ser Ser His Ala
 305 310 315 320

His Thr Asn Asn Phe Ala Lys Ser Val Val Asn Leu Val Asp Ser Ile
 325 330 335

Tyr Lys Glu Gln Leu Asn Thr Arg Val Val Leu Val Ala Val Glu Thr
 340 345 350

Trp Thr Glu Lys Asp Gln Ile Asp Ile Thr Thr Asn Pro Val Gln Met
 355 360 365

Leu His Glu Phe Ser Lys Tyr Arg Gln Arg Ile Lys Gln His Ala Asp
 370 375 380

Ala Val His Leu Ile Ser Arg Val Thr Phe His Tyr Lys Arg Ser Ser
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Leu Ser Tyr Phe Gly Gly Val Cys Ser Arg Thr Arg Gly Val Gly Val
 405 410 415

Asn Glu Tyr Gly Leu Pro Met Ala Val Ala Gln Val Leu Ser Gln Ser

130

420

425

430

Leu Ala Gln Asn Leu Gly Ile Gln Trp Glu Pro Ser Ser Arg Lys Pro
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Lys Cys Asp Cys Thr Glu Ser Trp Gly Gly Cys Ile Met Glu Glu Thr
450 455 460

Gly Val Ser His Ser Arg Lys Phe Ser Lys Cys Ser Ile Leu Glu Tyr
465 470 475 480

Arg Asp Phe Leu Gln Arg Gly Gly Ala Cys Leu Phe Asn Arg Pro
485 490 495

Thr Lys Leu Phe Glu Pro Thr Glu Cys Gly Asn Gly Tyr Val Glu Ala
500 505 510

Gly Glu Glu Cys Asp Cys Gly Phe His Val Glu Cys Tyr Gly Leu Cys
515 520 525

Cys Lys Lys Cys Ser Leu Ser Asn Gly Ala His Cys Ser Asp Gly Pro
530 535 540

Cys Cys Asn Asn Thr Ser Cys Leu Phe Gln Pro Arg Gly Tyr Glu Cys
545 550 555 560

Arg Asp Ala Val Asn Glu Cys Asp Ile Thr Glu Tyr Cys Thr Gly Asp
565 570 575

Ser Gly Gln Cys Pro Pro Asn Leu His Lys Gln Asp Gly Tyr Ala Cys
580 585 590

Asn Gln Asn Gln Gly Arg Cys Tyr Asn Gly Glu Cys Lys Thr Arg Asp
595 600 605

Asn Gln Cys Gln Tyr Ile Trp Gly Thr Lys Ala Ala Gly Ser Asp Lys
610 615 620

Phe Cys Tyr Glu Lys Leu Asn Thr Glu Gly Thr Glu Lys Gly Asn Cys
625 630 635 640

Gly Lys Asp Gly Asp Arg Trp Ile Gln Cys Ser Lys His Asp Val Phe

645

650

655

Cys Gly Phe Leu Leu Cys Thr Asn Leu Thr Arg Ala Pro Arg Ile Gly
 660 665 670

Gln Leu Gln Gly Glu Ile Ile Pro Thr Ser Phe Tyr His Gln Gly Arg
 675 680 685

Val Ile Asp Cys Ser Gly Ala His Val Val Leu Asp Asp Asp Thr Asp
 690 695 700

Val Gly Tyr Val Glu Asp Gly Thr Pro Cys Gly Pro Ser Met Met Cys
 705 710 715 720

Leu Asp Arg Lys Cys Leu Gln Ile Gln Ala Leu Asn Met Ser Ser Cys
 725 730 735

Pro Leu Asp Ser Lys Gly Lys Val Cys Ser Gly His Gly Val Cys Ser
 740 745 750

Asn Glu Ala Thr Cys Ile Cys Asp Phe Thr Trp Ala Gly Thr Asp Cys
 755 760 765

Ser Ile Arg Asp Pro Val Arg Asn Leu His Pro Pro Lys Asp Glu Gly
 770 775 780

Pro Lys Gly Pro Ser Ala Thr Asn Leu Ile Ile Gly Ser Ile Ala Gly
 785 790 795 800

Ala Ile Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe
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Lys Asn Val Lys Lys Arg Arg Phe Asp Pro Thr Gln Gln Gly Pro Ile
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32

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<220>
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35

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30

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26

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33

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Asp Tyr Ser His Cys Gln Gly Asn Arg Trp Arg Arg Ser Lys Arg Ala
 20 25 30

Ser Tyr Val Ser Asn Pro Ile Cys Lys Gly Cys Leu Ser Cys Ser Lys
 35 40 45

Asp Asn Gly Cys Ser Arg Cys Gln Gln Lys Leu Phe Phe Leu Arg
 50 55 60

Arg Glu Gly Met Arg Gln Tyr Gly Glu Cys Leu His Ser Cys Pro Ser
 65 70 75 80

Gly Tyr Tyr Gly His Arg Ala Pro Asp Met Asn Arg Cys Ala Arg Cys
 85 90 95

Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys Asp Phe Cys Thr Lys
 100 105 110

Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg Cys Phe Asp Glu Cys
 115 120 125

Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met Glu Cys Val Glu Gly
 130 135 140

Cys Glu Val Gly His Trp Ser Glu Trp Gly Thr Cys Ser Arg Asn Asn
 145 150 155 160

Arg Thr Cys Gly Phe Lys Trp Gly Leu Glu Thr Arg Thr Arg Gln Ile
 165 170 175

Val Lys Lys Pro Val Lys Asp Thr Ile Leu Cys Pro Thr Ile Ala Glu
 180 185 190

Ser Arg Arg Cys Lys Met Thr Met Arg His Cys Pro Gly Gly Lys Arg
195 200 205

Thr Pro Lys Ala Lys Glu Lys Arg Asn Lys Lys Lys Arg Lys Leu
210 215 220

Ile Glu Arg Ala Gln Glu Gln His Ser Val Phe Leu Ala Thr Asp Arg
225 230 235 240

Ala Asn Gln

<210> 49

<211> 29

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<213> Artificial/Unknown

<220>

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29

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aga tgt gca aga tgc aga ata gaa aac tgt gat tct tgc ttt agc aaa Arg Cys Ala Arg Cys Arg Ile Glu Asn Cys Asp Ser Cys Phe Ser Lys 95 100 105	338
gac ttt tgt acc aag tgc aaa gta ggc ttt tat ttg cat aga ggc cgt Asp Phe Cys Thr Lys Cys Lys Val Gly Phe Tyr Leu His Arg Gly Arg 110 115 120	386
tgc ttt gat gaa tgt cca gat ggt ttt gca cca tta gaa gaa acc atg Cys Phe Asp Glu Cys Pro Asp Gly Phe Ala Pro Leu Glu Glu Thr Met 125 130 135	434
gaa tgt gtg gaa gga tgt gaa gtt ggt cat tgg agc gaa tgg gga act Glu Cys Val Glu Gly Cys Glu Val Gly His Trp Ser Glu Trp Gly Thr 140 145 150 155	482
tgt agc aga aat aat cgc aca tgt gga ttt aaa tgg ggt ctg gaa acc Cys Ser Arg Asn Asn Arg Thr Cys Gly Phe Lys Trp Gly Leu Glu Thr 160 165 170	530
aga aca cgg caa att gtt aaa aag cca gtg aaa gac aca ata ctg tgt Arg Thr Arg Gln Ile Val Lys Lys Pro Val Lys Asp Thr Ile Leu Cys 175 180 185	578
cca acc att gct gaa tcc agg aga tgc aag atg aca atg agg cat tgt Pro Thr Ile Ala Glu Ser Arg Arg Cys Lys Met Thr Met Arg His Cys 190 195 200	626
cca gga ggg aag aga aca cca aag gcg aag gag aag agg aac aag aaa Pro Gly Gly Lys Arg Thr Pro Lys Ala Lys Glu Lys Arg Asn Lys Lys 205 210 215	674
aag aaa agg aag ctg ata gaa agg gcc cag gag caa cac agc gtc ttc Lys Lys Arg Lys Leu Ile Glu Arg Ala Gln Glu Gln His Ser Val Phe 220 225 230 235	722
cta gct aca gac aga gct aac caa taaaacaaga gatccggtag attttttaggg Leu Ala Thr Asp Arg Ala Asn Gln 240	776
gtttttgtt ttgcaaatgt gcacaaagct actctccact octgcacact ggtgtgcagc	836
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catggccct gtgttattt tgcatttgatt tgaatctgga gactgtgaag gcaggagtaa	956
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gaaagaagat gcttggcagg caatgogcta ctcactcgtg acctttatccatgtt ctcacattgt	1136